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CURRENT ISSUES IN ENT INFECTIOUS DISEASE

Editor
GEORGE A. GATES, MD

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CURRENT ISSUES IN ENT INFECTIOUS DISEASE

Editor

GEORGE A. GATES, MD

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SYMPOSIUM PARTICIPANTS

Charles D. Bluestone, MD
Professor of Otolaryngology
University of Pittsburgh School of Medicine
Director, Department of Pediatric Otolaryngology
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

Itzhak Brook, MD, MSc
Professor of Pediatrics and Surgery
Uniformed Services University
of the Health Sciences
Senior Investigator
Armed Forces Radiobiology Research Institute
Bethesda, Maryland

George A. Gates, MD
Professor and Vice-Chairman
Department of Otolaryngology–
Head and Neck Surgery
Washington University School of Medicine
St Louis, Missouri

G. Scott Giebink, MD
Professor of Pediatrics
and Otolaryngology
University of Minnesota School of Medicine
Minneapolis, Minnesota

Scott C. Manning, MD
Assistant Professor
Department of Otolaryngology
University of Texas Southwestern
Medical Center at Dallas
Director of Otolaryngology Service
Parkland Memorial Hospital
Dallas, Texas

Gerald Medoff, MD
Professor of Medicine
Professor of Microbiology and Immunology
Director, Mycology Center
Co-Director, Infectious Disease Division
Washington University School of Medicine
St Louis, Missouri

Jack L. Paradise, MD
Professor of Pediatrics
University of Pittsburgh School of Medicine
Medical Director
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

William J. Richtsmeier, MD, PhD
Associate Professor of Otolaryngology–
Head and Neck Surgery
Associate Professor of Oncology
Chief, Division of Head and Neck
Cancer Research
Johns Hopkins Medical Institutions
Baltimore, Maryland

Ellen R. Wald, MD
Professor of Pediatrics
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Randal S. Weber, MD
Assistant Professor of Surgery
Department of Head and Neck Surgery
University of Texas M. D. Anderson
Cancer Center
Houston, Texas

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INTRODUCTION

When antimicrobial agents became available in the early 1940s, more than one medical prophet predicted that the specialty of otolaryngology would cease to exist since the cure for infection had been discovered. Little did these sages envision the growth of the specialty into noninfectious areas, nor did they anticipate bacterial resistance, the problems of chronic infection, and the emergence of new infectious agents, eg, human immunodeficiency virus. Thus, the infectious disease aspects of the ears, nose, and throat remain an important part of the daily work of otolaryngologists and their colleagues in pediatrics and internal medicine.

It is to this important topic that this collection of papers is addressed. The presentations were given at a symposium, Current Issues in ENT Infectious Disease, sponsored by Beecham Laboratories (now SmithKline Beecham Laboratories) in March of 1990. I had the honor of organizing the program and choosing the topics and the speakers. Fortunately for both the attendees and the readers of this review, the speakers are among the most expert and best-recognized workers in infectious diseases of the ears, nose, and throat, and their papers provide up-to-date reviews of their respective topics. I am sure readers will agree with me that the relevance of these reports to daily practice is high.

George A. Gates, MD
Editor

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ANTIMICROBIAL USE IN OTOLARYNGEAL INFECTIONS: GENERAL CONSIDERATIONS

GERALD MEDOFF, MD

ST LOUIS, MISSOURI

With the development of numerous new antimicrobials and the improved efficacy of existing agents, more infections are being treated successfully, but the benefits of one agent over another have become an issue of subtle distinctions. Some clinical studies of new drugs have inherent drawbacks in their design and may not yield a comprehensive picture of antimicrobial characteristics in a wide range of patient types and diseases. Studies should therefore be carefully evaluated to determine whether a real advantage exists for a new agent. At Barnes Hospital (St Louis, Missouri), antimicrobials are chosen for the formulary on the basis of efficacy, toxicity, and cost. One or two agents are selected from a group of "therapeutic equivalents." Nonformulary agents or uses must be approved by the infectious disease staff. Evaluation and discussion of therapy with formulary and nonformulary drugs educates house staff, who can then use approved agents with greater knowledge and skill.

KEY WORDS — antibiotics, formularies, study design.

INTRODUCTION

The following case represents the first clinical trial of penicillin.[1] A 43-year-old policeman had had a sore on his lips for 4 months, from which a combined staphylococcal and streptococcal septicemia developed. He had multiple abscesses on his face and both orbits, osteomyelitis of the right humeral head with draining sinuses, and multiple lung abscesses. He was in great pain and was desperately ill. Sulfapyridine was tried without benefit, and a severe drug rash secondary to use of this antibiotic developed. Penicillin treatment was started on February 12, 1941, initially with 200 mg (10,000 U) intravenously, and then 100 mg every 3 hours. Striking improvement occurred after 24 hours. After 5 days, the patient was vastly better, afebrile, and eating well, and there was marked resolution of the abscesses on his face and scalp and in his right orbit.

Unfortunately, this historic trial terminated abruptly when the total supply of penicillin was exhausted by the 5-day course of treatment. After 10 days the infection recurred. The patient died 16 days later.

This elegant, although ultimately tragic, experiment represents a clinical paradigm in regard to demonstration of drug efficacy and superiority of a new therapy (penicillin) over that previously available. Since that time, it has become increasingly difficult to demonstrate superiority of new agents over those already in use. As new agents with increasingly broad spectrums are developed, more infections are being treated effectively, and since adequate therapy is available for almost all infections, a placebo-controlled study cannot be justified. New agents are therefore compared with old, and the differences between them have become more subtle, with comparisons focusing on factors such as isolated rare organisms included in the treatment spectrum, protein binding, half-life, and theoretic considerations about penetration into cells. This paper reviews how drug studies demonstrating these differences are conducted, as well as some of the difficulties inherent in them; describes how we at Barnes Hospital (St Louis, Missouri) choose among the numerous antimicrobials available; and, finally, suggests what issues need to be addressed in the advancement of antimicrobial therapy in the future.

DRUG STUDIES

According to standard drug study design, after in vitro studies have shown that a new agent is active, efficacy and toxicity are evaluated in at least two animal models. If the animal studies show positive results, the antibiotic is tested on human subjects. After evaluation for toxicity and pharmacokinetics in healthy controls, the agent is given to patients with infections. These studies generally have little relevance to treatment of very ill patients with severe infections; it is customary to start clinical trials with patients who have diseases such as urinary tract infections that are not overtly life-threatening. Such infections will be cured by almost any agent that is active against the causative bacteria, provided the drug is excreted in the urine in therapeutic concentrations.

Other noncomparative studies involve patients with such conditions as pneumonia or soft tissue or bone infection. Often, each trial includes only a small number of patients. The principal purpose of these trials is to determine optimal dosage and to measure toxicity, but a reasonably accurate evaluation of efficacy can also be obtained.

Once efficacy in human infection has been ascer-

From the Infectious Disease Division and Mycology Center, Washington University School of Medicine, St Louis, Missouri.

REPRINTS — Gerald Medoff, MD, Washington University School of Medicine, Box 8051, 660 S Euclid, St Louis, MO 63110.

tained and the drug has been shown to have an acceptable level of toxicity, trials are conducted to show that the antibiotic offers some advantage over those with similar properties that are presently in use. Such trials demonstrate one or all of the following about the new agent: that it 1) is more efficacious than existing drugs, 2) is less toxic, 3) has a pharmacologic advantage, and/or 4) is less costly.

In general, evaluation of these comparative studies is a difficult task for several reasons. Many studies do not include sufficient numbers of patients to show significant differences between antibiotics. This is particularly true in studies involving seriously ill patients with complex problems; paradoxically, these are frequently the patients for whom the drug is designed. For example, very few studies include large numbers of patients with bacteremia due to *Pseudomonas* or other virulent pathogens; therefore, comparisons between the results of treatment with the old and new antibiotics frequently cannot be fairly evaluated. Many studies show small differences in the outcome of treatment of staphylococcal and gram-negative bacillary infection, and large numbers of cases are needed in each study to show significance. The implication is that differences that do exist are small.

Studies with small numbers of subjects and short follow-up often do not provide enough data to evaluate adverse reactions. Thus, it is unwise to make optimistic claims of low toxicity before a drug is marketed and used for several years. In addition, the complexity of coexisting conditions in the subjects of some trials makes evaluation difficult. How does the clinician learn about toxic reactions resulting in neutropenia, bleeding disorders, abnormalities of liver and kidney function, and skin rash when the patient is a transplant recipient or has a malignancy and is receiving other medications that may cause reactions similar to those associated with the study drug? It is even more difficult to evaluate subtler toxicities such as bacterial resistance, secondary infection, or diarrhea caused by *Clostridia difficile*.

Studies often involve investigators and subjects from several different centers. This factor introduces problems such as nonuniformity of data and patients, variability of disease, and a lower level of quality control than in a single-site study. Studies may also emphasize easily treated infections instead of proven infections by problem organisms such as *Pseudomonas*, *Serratia*, and *Enterobacter*; therefore, cases that are not actually proven infections may be included.

All studies have strict criteria for inclusion of cases, and an extremely important part of any study design is the definition of what cases can and cannot be evaluated. Patients are considered unsuitable for evaluation, and are excluded from the study data, if the infecting organism is later determined to be resistant to the antibiotic being tested. While this practice is valid from the standpoint of study design, clinicians need to know about the incidence of such resistance in order to determine the ultimate clinical usefulness of that therapeutic regimen. In a sense, good results against susceptible bacterial strains have little meaning in an empiric therapy situation. Another common study criterion is a 4- to 5-day minimum period of treatment for inclusion of data. Frequently, information about patients who die before this time is excluded, yielding to data that favor positive results with the study drug.

It is up to the clinician to review studies with an eye toward whether a protocol yields a fair trial, and whether the results are interpreted correctly. Many studies are well designed and draw valid conclusions; others may be less reliable but still contain useful information. Well-run studies often lead to availability of new antibiotic agents with a valid and valuable medical purpose.

ANTIMICROBIAL CHOICES: BARNES HOSPITAL FORMULARY

Since it is impossible to include all available antibiotics in any hospital formulary, a decision must be made about how to choose among them. At Barnes Hospital, we use microbiologic data and sensitivity patterns of organisms, critical interpretations of relevant studies, and cost and other attributes as a basis for making our decisions. Using this information, we categorize groups of similar antibiotics as therapeutic equivalents. We then allow the hospital to choose one or two agents from each group of equivalents. We are also careful to control the use of certain drugs to prevent emergence of resistance. Once we have selected our formulary agents, we are careful to learn how to use them correctly, and to avoid making a change unless there is a compelling reason to do so. This system, which has been in operation since 1985,[2,3] has proven to be an effective teaching device for our house staff and private physicians. Moreover, antibiotic costs have decreased every year since its inception.

The Barnes Hospital formulary includes an established list of antibiotic classifications (see Table). In every case, formulary selection was primarily based on patient need and drug efficacy. Antibiotics are assigned to one of three categories — restricted, controlled, and nonrestricted — on the basis of therapeutic efficacy, toxicity, and cost. In the case of generics or therapeutic equivalents, the least expensive drugs are stocked. Restricted antibiotics are removed from the formulary and can be obtained only with the permission of the infectious disease specialists. Controlled antibiotics are subject to an automatic 72-hour stop order. Treatment with these agents can be continued beyond this time only if certain criteria are fulfilled, and only with per-

BARNES HOSPITAL ANTIBIOTIC FORMULARY SELECTIONS

Antibiotic	*Status*	*Comments*
Cephalosporins		
Cefazolin sodium	Unrestricted	Every-6-h dosing restricted
Cephalothin	Nonformulary	
Cephapirin sodium	Nonformulary	
Cefoxitin sodium	Restricted	
Cefotetan	24-h auto-stop	>2 g/d restricted
Cefamandole nafate	Nonformulary	
Cefonicid sodium	Nonformulary	
Cefuroxime axetil	Nonformulary	Oral dosing
Ceftazidime	72-h auto-stop	
Ceftriaxone sodium	72-h auto-stop	
Cefotaxime sodium	Restricted	
Cefoperazone sodium	Nonformulary	
Ceftizoxime sodium	Nonformulary	
Moxalactam	Nonformulary	
Penicillins		
Ampicillin	Unrestricted	
Amoxicillin	Unrestricted	
Oxacillin sodium	Unrestricted	
Nafcillin sodium	Restricted	
Methicillin sodium	Nonformulary	
Mezlocillin sodium	Unrestricted	>16 g/d restricted
Ticarcillin disodium	Restricted	
Carbenicillin (IV)	Restricted	
Carbenicillin indanyl sodium (oral)	Unrestricted	
Piperacillin sodium	Nonformulary	
Aminoglycosides		
Gentamicin sulfate	Unrestricted	
Amikacin sulfate	72-h auto-stop	Inhalation unrestricted for lung therapy
Netilmicin sulfate	Nonformulary	
Tobramycin sulfate	Nonformulary	Inhalation unrestricted for lung therapy
Miscellaneous		
Amoxicillin–clavulanate potassium	Nonformulary	
Ampicillin-sulbactam	Restricted	
Aztreonam	Restricted	
Ciprofloxacin	Restricted	
Clindamycin phosphate (IV)	Restricted	
Clindamycin hydrochloride (oral)	Unrestricted	
Imipenem–cilastatin sodium	Restricted	
Ticarcillin disodium–clavulanate potassium	Restricted	
Metronidazole	Unrestricted	
Norfloxacin	Restricted	
Vancomycin hydrochloride	72-h auto-stop	Oral dosing restricted

mission of the infectious disease group. Criteria for use of controlled and restricted antibiotics are explicit, and enforcement and education efforts are vigorous. For example, vancomycin hydrochloride (Vancocin) and amikacin sulfate (Amikin) are used only if the patient shows intolerance to the appropriate unrestricted antibiotics, or if a culture is positive for bacteria sensitive only to these drugs.

Members of the infectious disease division teach sessions on antibiotic use for the house and attending staff of Barnes Hospital. These sessions review the pharmacokinetics and toxicities of newer antibiotics, compare the new drugs with older equivalents, and recommend indications for use of specific antibiotics.

We have found that formulary restrictions, when combined with strict enforcement and physician education, can achieve significant cost savings with no negative effect on patient care. An interesting spin-off of our policy is its educational impact on house staff and physicians. Requests for use of restricted or controlled antibiotics frequently develop into useful teaching sessions about actual clinical problems, increasing the success of the program by emphasizing the reasons for not using a restricted antibiotic, and by ensuring that the correct drug is chosen in its place. In addition, dosage modifications are carried out on certain drugs when the physician has requested an inappropriate dosage. For example, repeated doses of cefazolin sodium (Ancef, Kefzol) at intervals of less than 8 hours require approval from an infectious disease physician.

PRESENT NEEDS

It is hoped that antimicrobial agents now in the development and marketing stages will meet clinicians' most pressing needs and become valuable additions to hospital formularies. At present, these needs include better treatment of infections caused by penicillin-resistant pneumococci, methicillin sodium–resistant *Staphylococcus aureus*, and resistant enterococcal and certain highly resistant gram-negative bacilli; better initial nontoxic empiric therapy for potentially life-threatening infections, including those occurring in immunocompromised patients; better treatment of certain deep infections that occur with implants and prosthetic devices; better treatment of polymicrobial infections; and more economical new agents.

SUMMARY

In the case of antimicrobials, new does not necessarily mean better, and a conservative approach to their use is desirable. Clinicians should learn to use a limited number of antibiotics and to understand their specific toxicities, limitations, and advantages. Studies of new agents should be evaluated carefully, and changes in prescribing made only for very good reasons. Because so many agents are available, and choices can be complex, we at Barnes Hospital have allowed the "experts," our infectious disease staff, to make these decisions by establishing our formulary and refereeing use of restricted and controlled drugs. While this particular program is only one possible way to structure criteria for antimicrobial choice, formal evaluation and monitoring of the use of such agents should be part of the policy of every medical institution.

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DIAGNOSIS AND MANAGEMENT OF ANAEROBIC INFECTIONS OF THE HEAD AND NECK

ITZHAK BROOK, MD, MSC
BETHESDA, MARYLAND

Anaerobic bacteria are important pathogens in head and neck infections such as chronic otitis media, chronic sinusitis, chronic mastoiditis, head and neck abscesses, cervical adenitis, parotitis, and postoperative infection. *Bacteroides* sp (*Bacteroides melaninogenicus* group, *Bacteroides oralis*, and *Bacteroides fragilis* group), *Peptostreptococcus* sp, and *Fusobacterium* sp predominate. The observed recent increase in the number of β-lactamase–producing strains of *Bacteroides* sp isolated in head and neck infections has been associated with increased failure rates of the penicillins in the management of these infections. The pathogenicity of these organisms is expressed through their ability not only to survive penicillin therapy but also to shield penicillin-susceptible pathogens from the drug. Because of these direct and indirect virulent characteristics of anaerobic bacteria, appropriate antimicrobial therapy must be directed against all pathogens in mixed infections.

KEY WORDS — anaerobic bacteria, head and neck infection, penicillin resistance.

INTRODUCTION

Anaerobic bacteria have an important causative role in head and neck infections, especially in many chronic forms. Their isolation in these infections is partially due to their predominance in the normal microflora of the oral mucous membranes.[1] The number of anaerobic bacteria in saliva is 1.1 x 10^8/mL, compared with the aerobic count[2] of 4 x 10^7/mL — a 10:1 ratio in the oral cavity.[3] Anaerobes usually recovered from the nasopharynx as part of the normal flora and as pathogens in head and neck infections are *Bacteroides* sp (including *Bacteroides melaninogenicus* group and *Bacteroides oralis*), *Peptostreptococcus* sp, and *Fusobacterium* sp.

In studies that used proper techniques for transportation, cultivation, and identification, anaerobes have been isolated in acute[4] and chronic[5-7] otitis media (OM), tonsillar and retropharyngeal abscesses,[8] recurrent tonsillitis,[9] suppurative thyroiditis[10] and parotitis,[11] chronic sinusitis,[12] cervical lymphadenitis,[13] odontogenic infections,[14] and infections following head and neck operations.[15]

In most of these infections, a polymicrobial aerobic-anaerobic flora can be recovered from the infected site. Presence of mixed flora allows a synergistic relationship between the different organisms that facilitates their virulence[16] and enables them to benefit from a metabolic enzymatic relationship. Anaerobic bacteria possess several virulence factors. These include the presence of a capsule[17] and the ability to adhere to mucosal epithelial cells and produce superoxide dismutase and catalase, immunoglobulin proteases, and coagulation-promoting and coagulation-spreading factors (such as hyaluronidase, collagenase, and fibrinolysin).[1] This review describes anaerobic bacteria as a factor in head and neck infections. Since many anaerobic as well as aerobic organisms produce β-lactamase, which may interfere with the activity of penicillin and protect penicillin-susceptible organisms from this drug,[18] management of infections in the presence of β-lactamase is also discussed.

OTITIS MEDIA

Awareness of the importance of anaerobic bacteria in ear infections and recognition of their role has increased in recent years. This knowledge can influence management decisions, since some of these organisms are resistant to various antimicrobials. The predominance of anaerobic organisms in the oral flora explains their involvement in OM. Their recovery correlates with the use of proper and adequate techniques of collection, transportation, and inoculation of specimens — techniques that were not used in many past studies of acute, serous, and chronic OM.[19] When such methods were used, however, anaerobic organisms were recovered in substantial numbers.[20]

Acute Otitis Media. In a study of children with acute OM,[21] anaerobes, mainly *Peptostreptococcus* sp, were recovered in about one fourth of 186 ear aspirates. In about one third of the cases, these organisms were mixed with aerobic and facultative bacteria. Organisms were isolated in over 90% of patients; a larger percentage had been found in other studies, in which methods for recovery of anaerobes were not used.[1] Since the anaerobes isolated in acute OM are susceptible to the penicillins as well as other antimicrobials commonly used for treatment, no change in recommended therapy is indicated. Further studies are warranted, however, to elucidate the precise role of anaerobes in this type of infection.

From the Uniformed Services University of the Health Sciences and the Armed Forces Radiobiology Research Institute, Bethesda, Maryland. The opinions and assertions contained herein are the private ones of the writer, and are not to be construed as official or reflecting the views of the Department of Defense, the Navy Department, or the Naval Service at large.

REPRINTS — Itzhak Brook, MD, MSc, Armed Forces Radiobiology Research Institute, Bethesda, MD 20889-5145.

TABLE 1. FREQUENCY OF ANAEROBIC AND AEROBIC ORGANISMS RECOVERED IN CHRONIC SUPPURATIVE OTITIS MEDIA

Authors	*No. Anaerobes Recovered Per Total No. Cases*	*Anaerobic Cocci*	Bacteroides *sp*	Fusobacterium *sp*	Clostridium *sp*	Staphylococcus aureus	Pseudomonas *sp*	*Other Gram-Negative Rods*
Karma et al[23]	38/114 (33%)	15	29	2	2	32	16	37
Sugita et al[24]	62/760 (8%)	38	18	6	2	8	12	31
Ayyagari et al[25]	68/115 (59%)	33	43	7	6	22	29	32
Sweeney et al[26]	57/130 (44%)	7	54	9	1	33	25	86
Constable and Butler[27]	20/100 (20%)	9	7	—	—	29	15	34
Papastavros et al[28]	19/ 44 (43%)	10	12	—	—	2	20	4
Brook and Yocum[29]	35/ 68 (51%)	31	21	4	3	15	33	31

Otitis Media With Effusion. In a study of OM with effusion[22] in which methods for the cultivation of anaerobes were used, these microorganisms were isolated in 23 (40%) of 57 patients. Anaerobes were present as the only isolate in 17% of culture-positive specimens; in an additional 26% they were mixed with aerobes or facultative bacteria. The predominant anaerobes were *Peptostreptococcus* sp and *B melaninogenicus* group.

The role of aerobic and anaerobic microorganisms in the pathogenesis of OM with effusion is not yet clear; however, antimicrobial agents are often administered in an attempt to eradicate the microorganisms that are generally recovered in about half the effusions. The presence in serous ear aspirates of many microorganisms that produce β-lactamase raises the question of whether antibiotics effective against aerobic and anaerobic β-lactamase–producing bacteria should be used in treatment of OM with effusion. Controlled studies may define the value of antimicrobial therapy in patients with this type of infection and clarify the role of bacteria in pathogenesis of the inflammatory process.

Chronic Suppurative Otitis Media and Mastoiditis. The high number of negative cultures of aspirates from patients with chronic suppurative middle ear effusion in some studies may be due to the use of inappropriate methods of anaerobe recovery.[19]

Several studies report the recovery of anaerobes in about half of patients with chronic suppurative OM[5,6] (Table 1[23-29]) and those with cholesteatoma.[30,31] The variability in the rate of isolation of anaerobes in these studies may be attributed to differences in study locations and laboratory methods. In several studies, delays in cultivation were extensive and the length of incubation was inadequate for the recovery of anaerobic bacteria. The predominant anaerobes were *Bacteroides* sp, *Peptostreptococcus* sp, and *Fusobacterium* sp. Many of these organisms produced β-lactamase, which may have contributed to the failure of these patients to respond to penicillins. In a recent study,[29] the enzyme β-lactamase was detected in 84% of ear aspirates that contained β-lactamase–producing bacteria (BLPB) in excess of 10^{11}/mL. Anaerobic isolates were usually mixed with other anaerobic or aerobic bacteria, with the number of isolates per aspirate ranging from two to four.

Anaerobes are recovered in ear aspirates in most cases of infectious complications of chronic suppurative OM; this finding highlights their importance in this disease. Anaerobes similar to those recovered in chronic suppurative OM were isolated from 23 of 24 specimens (96%) obtained from patients with chronic mastoiditis.[7] Anaerobes were also recovered from most patients with intracranial abscesses complicating chronic suppurative OM.[1,20,32]

The efficacy of antibiotics against these organisms is shown by two studies in which infection was eradicated in 52%[29] to 89%[33] of treated patients. Since a control group was not included in these studies, further research could more carefully evaluate the efficacy of medical and surgical management.

Cholesteatoma accompanying chronic suppurative OM can induce the absorption of bone. Various theories have attempted to explain the process of expansion of cholesteatoma and the collagen degradation that occurs in its vicinity.[30] Production of organic acids by anaerobic bacteria may be involved in the destructive process.[30] Bacteria recovered in cases of cholesteatoma associated with chronic suppurative OM and in chronic purulent otitis media are similar. Thus, cholesteatoma may serve as a nidus of the chronic ear infection.[30]

Chronic mastoiditis is one of the serious complications that can follow chronic OM. In a study of 24 patients with chronic mastoiditis,[7] 20 (83%) had polymicrobial aerobic-anaerobic flora. The predominant isolates were anaerobic cocci, *Bacteroides* sp, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.

CHRONIC SINUSITIS

Anaerobes are often recovered in aspirates from chronically inflamed sinuses. Although they are generally isolated in only about 10% of patients with acute sinusitis, they can be recovered in up to two thirds of chronic infections.[1,20] When inflammation persists, oxygen tension is reduced and bicarbonate content is increased in the sinuses, facilitating the growth of anaerobes as the infection becomes chronic. The predominant anaerobes recovered are *Bacteroides* sp and *Peptostreptococcus* sp.[1,20] An average of three anaerobes per sinus aspirate were recovered in children[12] and adults[34] with chronic sinusitis. β-Lactamase production was noted in 12 of 121 (10%) of the isolates in children, and in 12 of 27 (44%) of those in adults.[34]

When not treated promptly and properly, sinus infection may spread directly or via anastomosing veins to nearby structures, including the central nervous system. The first warning sign of extension of the infection may be the appearance of orbital cellulitis.[35] Possible intracranial complications include meningitis, cavernous sinus thrombosis, and brain abscesses.[32] Response to antimicrobial therapy, even when appropriately administered, is often inadequate and unpredictable,[35] perhaps because of poor penetration of the antimicrobial into the infected sinus space and/or its inactivation by pus or β-lactamase.

Surgical drainage is of paramount importance, especially if no clinical improvement has occurred, and should not be delayed for more than 48 hours after antimicrobial therapy has been initiated. In many cases it should be an integral part of management.

PHARYNGOTONSILLITIS

Group A β-hemolytic streptococci (GABHS), *S aureus, Streptococcus pneumoniae,* and viruses are generally associated with tonsillar infections. However, anaerobes also have been isolated from the core of tonsils in children with recurrent GABHS[9] and non-GABHS[36] tonsillitis and peritonsillar[8] and retropharyngeal[37] abscesses. β-Lactamase–producing strains of *Bacteroides fragilis, Fusobacterium* sp, and *S aureus* were isolated from the tonsils of 74% of children with recurrent GABHS tonsillitis[9,38-40] and from 40% of children with non-GABHS tonsillitis.[36] Similar organisms were recovered from patients with adenoiditis and adenoid hypertrophy.[41]

The possible role of anaerobes in the acute inflammatory process in the tonsils is supported by several clinical observations: the recovery of anaerobes from abscesses of tonsils or the retropharyngeal area, in many cases without any aerobic bacteria[8,37]; their isolation in well-established anaerobic infections of the tonsils (ie, Vincent's angina)[1]; the increased recovery rate of encapsulated *B melaninogenicus* organisms from acutely inflamed tonsils[42]; their isolation from the core of recurrently inflamed non-GABHS tonsils[36]; the response to antibiotics in patients with non-GABHS tonsillitis[43,44]; and the recently observed elevated antibody titers to *Bacteroides intermedius* in patients with recurrent tonsillitis.[45]

TABLE 2. FAILURE RATES IN THERAPY OF RECURRENT GROUP A STREPTOCOCCAL PHARYNGITIS

	Failure Rate	
Authors	*Penicillins*	*Other Drugs*
Brook and Hirokawa[47]	13/15 (87%)	Erythromycin 9/15 (60%) Clindamycin 1/15 (7%)
Kaplan and Johnson[48]	17/24 (71%)	Amoxicillin–clavulanic acid 2/21 (10%)
Brook[49]	6/20 (30%)	Amoxicillin–clavulanic acid 0/20 (0%)

Recurrent pharyngotonsillitis due to GABHS is still a serious clinical problem. Failure to eradicate the streptococci from patients treated with penicillin can occasionally lead to rheumatic fever and, rarely, to glomerulonephritis. As a last resort, many physicians refer their patients for elective tonsillectomy.

One explanation for penicillin failure in such cases is the shift in oral microbial flora that occurs with repeated administration of penicillin. This results in selection of BLPB, eg, strains of *Hemophilus* sp, *S aureus, Moraxella catarrhalis,* and *Bacteroides* sp[18] that, by degrading penicillin in the area of the infection, can protect not only themselves but also penicillin-susceptible pathogens. The role of these organisms in the inability of penicillin to eradicate GABHS tonsillitis is supported by recovery of aerobic and anaerobic BLPB in over three fourths of patients with recurrent GABHS tonsillitis,[9,38-40] measurable β-lactamase activity in the core of tonsils in such cases,[46] and the response of such infections to antimicrobials effective against BLPB (ie, clindamycin [Cleocin] or amoxicillin–clavulanate potassium [Augmentin][16,47-49]; Table 2[47-49]).

ODONTOGENIC INFECTIONS

The bacteria isolated from odontogenic infections generally reflect the host's indigenous oral microflora.[2] The microorganisms commonly isolated are *Bacteroides* sp, *Peptostreptococcus* sp, and *Fusobacterium* sp. The anaerobic black-pigmented gram-negative bacilli receive the most attention among the bacteria potentially associated with oral and dental infection.[1] *Bacteroides gingivalis* and *B intermedius* are the organisms most frequently isolated from periodontal lesions. Other groups of bacteria, however, are also consistently recovered from odontogenic infections; this finding suggests that many pathogens may be capable of producing clinical signs and symptoms of illness.

Anaerobic bacteria have been recovered from patients with dentoalveolar abscesses.[2] Studies from the preantibiotic era of acute and chronic alveolar abscesses document the recovery of predominantly aerobic streptococci; fusiform bacilli and *Bac-*

TABLE 3. CORRELATION BETWEEN PREDISPOSING CONDITIONS AND BACTERIA RECOVERED FROM 67 ABSCESSES

		Type of Bacterial Growth			*No. Isolates of Predominant Microorganisms Recovered*				
Predisposing Conditions	*No. Patients*	*Aerobes Only*	*Anaerobes Only*	*Aerobes and Anaerobes*	Staphylococcus aureus	*Group A Streptococci*	*Anaerobic Cocci*	Bacteroides *sp*	Fusobacterium *sp*
Dental infection or manipulation	9	—	6	3	2	—	7	8	3
Tonsillitis	6	—	2	4	2	4	4	6	4
Trauma	13	11	—	2	8	1	1	2	—
Congenital cyst	3	—	2	1	1	—	2	1	—
Fetal monitoring	5	—	3	2	—	—	2	3	1
Unknown	31	24	2	5	15	3	1	3	1
Total	67	35	15	17	28	8	17	23	9

Adapted from Brook.[53]

teroides sp were also isolated. More recent studies, however, report the isolation of a variety of gram-positive and gram-negative anaerobes in periodontal abscesses.[1]

In a recent quantitative study of 50 dentoalveolar abscesses, Lewis et al[50] found 3.3 isolates per abscess. Twenty (40%) abscesses contained anaerobes only, and 27 (54%) had a mixture of both aerobes and anaerobes. Strict anaerobes, the most common being *Peptostreptococcus* sp, *B oralis,* and *B melaninogenicus,* were recovered from 38 (76%) of patients.

Anaerobic organisms outnumbered aerobes eight to one in a study of the bacteriology of periodontal abscesses in 12 children.[14] Four β-lactamase–producing organisms were recovered from four patients (33%); these were three of the nine *B melaninogenicus* isolates and one of the three *B oralis* isolates.

DEEP FASCIAL SPACE INFECTIONS

Odontogenic infections that originate from infected or necrotic pulp may spread to the adjacent deep fascial spaces of the upper neck and lower head. In Ludwig's angina, a bilateral infection of the submandibular, sublingual, and deep neck spaces, a variety of organisms have been isolated. These include mostly anaerobic bacteria such as *Bacteroides* sp, *Fusobacterium* sp, and cocci. Often, one or more aerobic organisms have also been recovered: staphylococci, streptococci, pneumococci, *Escherichia coli,* Vincent's spirochetes, *Hemophilus influenzae,* and *Candida.*

PURULENT NASOPHARYNGITIS

Nasopharyngitis is generally due to viral infection. However, *S pneumoniae, H influenzae, S aureus,* and *Streptococcus pyogenes* are often isolated from the purulent discharge.[51] A recent study described the isolates of aerobic and anaerobic bacteria in purulent nasopharyngitis.[52] Specimens were obtained from the inferior nasal meatus of 25 children with purulent nasopharyngitis and from 25 controls. Bacteria recovered in significantly higher numbers from patients with nasopharyngitis were *S pneumoniae, Hemophilus* sp, *Bacteroides* sp, *Peptostreptococcus* sp, and *Fusobacterium* sp. The organism recovered significantly more often from controls was *Propionibacterium acnes.* These findings suggest a secondary role for the aerobic-anaerobic polymicrobial flora in purulent nasopharyngitis.

ABSCESSES OF HEAD AND NECK

Most studies have established *S aureus* and GABHS as the predominant pathogens in abscesses of the head and neck. A recent study of 36 children with abscesses of the neck and 31 with abscesses of the head illustrated the importance of anaerobes in head and neck infections.[53] In neck infections, aerobes only were recovered in 24 (67%), anaerobes in 7 (19%), and mixed aerobic and anaerobic bacteria in 5 (14%). In abscesses of the head, aerobes were recovered in 11 (35%), anaerobic bacteria in 8 (26%), and mixed aerobic and anaerobic bacteria in 12 (39%). The most common organism recovered in neck infections was *S aureus* (20 isolates), and in head infections, *Bacteroides* sp (19 isolates) (Table 3[53]). β-Lactamase–producing bacteria were recovered in 36 isolates from 31 of the 67 abscesses (46%). A higher recovery rate of anaerobes was observed in patients with dental infection or manipulation, tonsillitis, or fetal monitoring. *Staphylococcus aureus* was associated with trauma (Table 3). In this study, anaerobic bacteria were recovered with greater frequency in abscesses of the head than those of the neck and were generally recovered in polymicrobial infections, together with aerobic bacteria. Anaerobes were recovered with higher frequency in infections that originated from locations in which anaerobes were involved in chronic infections, such as teeth, sinuses, and tonsils.

TONSILLAR, PERITONSILLAR, AND RETROPHARYNGEAL ABSCESSES

Group A β-hemolytic streptococci often are known pathogens in tonsillar, peritonsillar, and retropharyngeal infections. *Staphylococcus aureus* and *S pneumoniae* are also found frequently; gram-negative organisms, rarely. Anaerobes have been identified in peritonsillar and retropharyngeal abscesses in studies that employed proper techniques for their cultivation.

In recent reports of aspiration from 16 children with peritonsillar abscesses (quinsy)[8] and of 14 children with retropharyngeal abscesses,[37] anaerobes were recovered in all cases. The predominant organisms were *B melaninogenicus*, *Peptostreptococcus* sp, *Fusobacterium* sp, *Streptococcus* sp, GABHS, *Hemophilus* sp, and *S aureus*. β-Lactamase–producing bacteria, including isolates of *S aureus*, *B melaninogenicus* group, and *B oralis*, were found in the majority of cases.

ACUTE SUPPURATIVE PAROTITIS

Staphylococcus aureus is the organism most commonly causing acute parotitis; *Streptococcus* sp and Enterobacteriaceae have also been reported, however.[54] Several case reports also describe the recovery of *B melaninogenicus* and *Peptostreptococcus micros* from infected parotid glands.[11,20]

A recent study[55] illustrates the polymicrobial nature and importance of anaerobic bacteria in acute suppurative parotitis. Aspirates of pus from 23 cases of acute suppurative parotitis were studied for aerobic and anaerobic bacteria. Anaerobic bacteria only were recovered in 10 (43%) patients, aerobes and facultatives were recovered in 10 (43%), and mixed anaerobic and aerobic flora were present in 3 (13%). The predominant isolates were *S aureus* (8 isolates), *Bacteroides* sp (6), and *Peptostreptococcus* sp (5). β-Lactamase–producing bacteria were recovered from 73% of the specimens.

CERVICAL LYMPHADENITIS

The rare isolation of anaerobes in cases of cervical adenitis has been reported.[20] Two studies that used proper methods of recovery illustrated the importance of anaerobes in cervical lymphadenitis.[13,56] Aerobes only were recovered from 27 (60%) of 45 aspirates, anaerobes alone from 8 (18%), and mixed aerobic and anaerobic bacteria from 9 (20%). β-Lactamase–producing bacteria were recovered from 15 (33%) of the 45 specimens.[13] Roberts and Linsey,[56] who isolated organisms in 35 nodes, found mycobacterial species in 22 (63%) specimens and bacteria in 11 (31%) cultures, 5 of which were anaerobic.

ACUTE SUPPURATIVE THYROIDITIS

Staphylococcus aureus, *S pyogenes*, *S epidermidis*, and *S pneumoniae* are the isolates most commonly found in suppurative thyroiditis in children. Rarely, *Klebsiella* sp, *H influenzae*, *Streptococcus* sp, *Salmonella* sp, and Enterobacteriaceae are found. *Bacteroides* sp and *Peptostreptococcus* sp may cause this infection,[10] as well as *Eikenella corrodens* and *Actinomyces* sp. In one study, polymicrobial infection was found in about one third of patients.[57]

WOUND INFECTIONS AFTER HEAD AND NECK SURGERY

Wound infections may occur after head and neck surgery, particularly after surgery for malignant tumors.[1] These infections, often polymicrobial, result from exposure of the surgical site to the oropharyngeal flora, and from compromise of the surgical site by decreased blood supply and necrotic tissues.[58]

Among 24 patients who developed postoperative wound infection after head and neck cancer surgery,[15] aerobic bacteria were recovered from 2 (8%), anaerobic bacteria from 1 (4%), and mixed aerobic and anaerobic isolates from 21 (88%). A total of 146 isolates (66 aerobic and 80 anaerobic) were recovered — an average of 6 isolates per specimen. The most frequently recovered isolates were *S aureus*, *Bacteroides* sp, *Peptostreptococcus* sp, *Fusobacterium* sp, and enteric gram-negative rods. Twenty-two isolates recovered from 17 (70%) wounds yielded BLPB, mostly *S aureus* and *B melaninogenicus* group.

CONCLUSION

Infections of the head and neck often involve mixed aerobic and anaerobic organisms. Anaerobes contribute to the severity and chronicity of infections that occur in the sinuses, the nose, and various other sites in and around the oral cavity.[18] Although surgical drainage is of primary importance, antimicrobial agents effective against both aerobic and anaerobic organisms are an integral part of therapy. Use of such agents is important not only to prevent chronicity, but also to prevent local and systemic extension of infection. Although penicillin is useful, the increase in penicillin resistance of many aerobic and anaerobic flora is of concern.[31,32] Therefore, in patients infected with BLPB, adding metronidazole (Flagyl, Protostat) to penicillin, or alternative therapy with clindamycin hydrochloride (Cleocin), cefoxitin sodium (Mefoxin), imipenem–cilastatin sodium (Primaxin), or the combination of a penicillin plus a β-lactamase inhibitor (Augmentin, Timentin) is justified.

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ANTIBIOTIC PROPHYLAXIS IN CLEAN-CONTAMINATED HEAD AND NECK ONCOLOGIC SURGERY

RANDAL S. WEBER, MD DAVID L. CALLENDER, MD
HOUSTON, TEXAS

The use of antibiotic prophylaxis in head and neck oncologic surgery has greatly reduced the risk of postoperative wound infection and the corresponding increase in morbidity and health care costs. Conversely, inappropriate perioperative use of antibiotics increases costs and risks to patients. Antibiotic prophylaxis is beneficial only in clean-contaminated head and neck surgery; targets are the bacterial flora that commonly inhabit the skin and upper aerodigestive tract, with antibiotics effective against gram-positive aerobic organisms and anaerobic organisms providing the best coverage. Maximum efficacy is achieved with immediate preoperative and short-term (< 48 hours) postoperative antimicrobial administration in adequate doses. Optimum benefit from prophylaxis in head and neck oncologic surgery depends on appropriate selection and administration of antibiotics in combination with sound, established surgical principles.

KEY WORDS — antibiotic prophylaxis, clean-contaminated wounds, oncologic head and neck surgery.

INTRODUCTION

One of the great advances in contemporary head and neck oncologic surgery has been the prevention of postoperative wound sepsis with the use of broad-spectrum antibiotics. Antibiotic prophylaxis has dramatically reduced morbidity from these procedures by lessening the incidence of infection. Decreased infection rates have, in turn, shortened duration of hospitalizations and decreased medical costs. Inappropriate use of antibiotics, however, increases medical expenditures and may result in patient sensitization to or superinfection by resistant organisms. Optimum benefit depends on the rational use of prophylactic antibiotics by the head and neck oncologic surgeon. This review discusses the proper use of prophylactic antibiotics based on bacteriologic studies and the results of clinical trials.

CLASSIFICATION AND DIAGNOSIS OF INFECTION

Surgical wounds may be classified in four categories according to criteria set forth by the National Academy of Sciences–National Research Council.[1] Classification indicates the relative risk of postoperative wound infection, based on the degree of contamination present at the time of operation. *Clean wounds* are made under ideal conditions in which no infection is present and no lapse in sterile technique occurs during the procedure (eg, routine thyroidectomy, neck dissection, and parotidectomy). *Clean-contaminated wounds* are sterile initially, but a mucosal barrier is crossed or a hollow viscus is entered during the operation (eg, laryngectomy and composite resection). *Contaminated wounds* are a result of a major lapse in sterile technique or exposure to acute nonpurulent inflammation. Fresh traumatic wounds are included in this category. *Dirty wounds* are infected traumatic wounds contaminated with bacteria or environmental debris.

Diagnosis of a postoperative wound infection after clean-contaminated head and neck surgery may be difficult, since nonspecific clinical signs that mimic infection often occur in the immediate postoperative period. Many patients develop wound erythema and induration secondary to lymphatic and venous stasis. Fever and leukocytosis are common, presumably because of microatelectasis; they usually respond to ambulation and attention to pulmonary toilet. Conclusive diagnosis of a wound infection depends on identification of purulence by observation of spontaneous wound discharge, needle aspiration of purulent material, or development of a mucocutaneous fistula.

ANTIBIOTIC PROPHYLAXIS

The need for antibiotic prophylaxis is dictated by the risk of infection for the particular type of wound. Unfortunately, evaluation and comparison of antibiotic prophylaxis trials are complicated because of the differing criteria used to define a wound infection.

Clean, Contaminated, and Dirty Wounds. Contaminated and dirty wounds are by definition either infected or at high risk for infection, making therapeutic antibiotic administration essential. The infection rate for clean wounds is 5% or less when prophylactic antibiotics are administered.[2] Johnson and Wagner,[3] in a retrospective review, found an infection rate of 0.9% in 175 patients undergoing parotidectomy without prophylactic antibiotics, compared with no infections in 55 patients who received prophylaxis — a difference that was not significant. The authors concluded that perioperative use of antibiotics was not beneficial or cost-effective for clean head and neck procedures. No randomized prospective study has been undertaken to determine the potential benefit of prophylactic antibiotics in

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From the Department of Head and Neck Surgery, University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — Randal S. Weber, MD, Dept of Head and Neck Surgery, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

clean head and neck procedures, and since the infection rate is very low for these types of wounds, an unfeasibly large sample size would be necessary to demonstrate a benefit from antibiotics. Overall analysis of risk versus benefit for antibiotic prophylaxis in clean head and neck procedures does not support its routine use.

Clean-Contaminated Wounds. Clean-contaminated wounds, the most frequent type encountered in oncologic surgery, are at a substantial risk for postoperative infection without antibiotic prophylaxis. In an early trial of perioperative antibiotic use in head and neck surgery, Ketcham et al[4] observed a 54.5% infection rate in clean-contaminated cases treated with placebo. Later investigations by other authors[5-9] reported infection rates ranging from 24% to 87% with placebo. These randomized, prospective studies clearly indicate a high risk for postoperative wound infection in patients undergoing clean-contaminated surgery without prophylaxis, making additional placebo-controlled trials unwarranted.

The benefit of antibiotic prophylaxis in clean-contaminated head and neck surgical procedures is substantiated by results of several randomized prospective trials. Ketcham et al[4] demonstrated the efficacy of perioperative administration of antibiotics in reducing wound sepsis. The infection rate among 9 patients receiving prophylactic chloramphenicol was 22.2% (2 patients), compared with 54.5% (6 patients) in 11 patients receiving placebo. Dor and Klastersky[6] conducted a double-blind prospective controlled trial comparing ampicillin and cloxacillin with placebo. With 52 patients in the antibiotic arm and 50 patients in the placebo arm, the infection rates were 17.3% (9 patients) and 36% (18 patients), respectively ($p < .05$). The predominant organisms cultured from infected wounds were gram-negative rods; however, *Staphylococcus aureus* was also isolated in several cases. A potential shortcoming of this study was the enteral administration of antibiotics, which can result in erratic absorption and unpredictable serum drug levels.

In 1979, Becker and Parell[7] reported the results of a randomized, double-blind study comparing placebo with cefazolin, 1 g preoperatively and four 1-g doses postoperatively, in 55 patients undergoing clean-contaminated head and neck operations. The infection rate among the patients receiving cefazolin was 38% (12 of 32 patients), compared with 87% (20 of 23 patients) for those in the placebo arm. Because of the dramatic and significant difference in infection rates between the two arms, the study was terminated early. The organism most frequently isolated was *S aureus* (30%); gram-negative rods were cultured in 37% of patients. Anaerobic cultures were not performed.

INCIDENCE OF WOUND INFECTION, BY TREATMENT

Antibiotic	*Dose*	*Duration (d)*	*No. of Patients*	*Infections*	
				No.	*%*
Cefazolin	500 mg	1	21	7	33
Cefazolin	500 mg	5	30	6	20
Clindamycin and gentamicin	300 mg and 1.7 mg/kg	1	29	2	7*
Clindamycin and gentamicin	300 mg and 1.7 mg/kg	5	27	1	4*

Modified from Johnson.[10]

*Significant decrease in infection rate compared with cefazolin ($p = .05$).

Johnson[10] has summarized the results of several studies comparing cefazolin (1 day versus 5 days) with a combination of clindamycin and gentamicin (1 day versus 5 days; see Table[10]). A significantly higher incidence of infections was found in patients treated with cefazolin ($p = .05$) than in those who received the combination regimen. However, the small number of patients in each arm and the use of a low dose of cefazolin may limit validity of the results. In another study, Johnson et al[9] randomized 118 patients to receive either moxalactam, a third-generation cephalosporin, or cefazolin, each in 2-g doses every 8 hours for a total of 4 doses. Wound infections developed in 7 patients (6%): 5 in the cefazolin arm and 2 in the moxalactam arm — a difference that was not significant. Although the sample size was relatively small, this study illustrates two important points. First, an adequate dose of antibiotic must be given to achieve tissue levels inhibitory to bacterial proliferation, hence the increased efficacy of a 2-g dose of cefazolin versus a 500-mg dose. Second, when different antibiotics are equally effective against the infecting organisms, no difference in infection rates will be seen.[11] The latter point suggests that the least toxic of drugs of comparable efficacy is the best choice for prophylaxis.

Bacteriologic Factors. If prophylaxis is to be successful, the organisms contaminating the wound at the time of operation must be targeted. Endogenous organisms in head and neck oncologic procedures include the skin flora, predominantly *S aureus*, *Staphylococcus epidermidis*, and β-hemolytic streptococci, and the commensal microorganisms of the upper aerodigestive tract. In the oropharyngeal secretions, anaerobic organisms are 10 times more common than aerobic organisms, with bacterial counts ranging from 10^8/mL to 10^9/mL.[12] These organisms, which colonize the tongue, teeth, and dental crevices, are exfoliated into the saliva. Among the anaerobic organisms, *Bacteroides melaninogenicus* and *Fusobacterium* species are found in high concentrations in dental crevices. The principal organisms in saliva that must be targeted are gram-positive aerobes and anaerobes; gram-negative aerobic organisms are not usually present in the saliva of normal individuals.[13] The addition of antibiotics specific to anaerobic organisms has been shown to decrease the incidence of postoperative wound infection in head and neck oncologic procedures. Robbins et al,[2] in a randomized prospective study, compared cefazolin alone to a combination of cefazolin and metronidazole. The latter is a nitroimidazole compound with no in vitro activity against gram-positive and gram-negative aerobic organisms. For prophylaxis, it must therefore be used in combination with another antibiotic. Among the 281 patients undergoing clean-contaminated operations, the infection rate was 11.9% for those receiving the combination regimen and 23.9% for the group receiving cefazolin alone ($p < .05$).

The bacteria colonizing a necrotic tumor may differ from normal upper aerodigestive tract flora and include pathogenic as well as nonpathogenic species.[13] Although gram-negative aerobes such as *Klebsiella, Pseudomonas,* and *Proteus* are not often present in the upper aerodigestive tract of normal controls, they may be readily obtained from preoperative tumor cultures.[14] Other organisms isolated from the tumor bed include *S aureus* and multiple streptococcal species.[15] Unfortunately, there is little correlation between results of cultures done preoperatively and those from infected wounds. In fact, several investigators[6,8,16,17] have found that wound infection develops in as many patients with negative preoperative cultures as in those with positive preoperative cultures. For example, Suarez Nieto et al[17] obtained perioperative cultures from 117 patients undergoing clean-contaminated head and neck surgery. Of the 18 (15%) patients in whom infection developed, 8 (44%) had had preoperative pathogens identified, whereas 10 (56%) had not.

It is an attractive assumption that the organisms isolated from a postoperative wound catheter drainage are predictive of the flora that might cause wound infection and thus provide a guideline for antibiotic selection. In practice, however, pathogens isolated from wound catheter drainage do not correspond to those recovered from the wound. Dor and Klastersky[6] reported that 21 of 52 patients had pathogens isolated from wound catheter drainage. Of patients with infections, all had pathogens isolated. However, pathogens were also isolated from 13 of 21 patients without infection. The same organisms were recovered from the wound and catheter drainage in only 8 (38%) of infected patients. Although Yoder and Silva[18] found a 100% correlation between bacterial isolates from catheter drainage and infecting organisms recovered from the wound, Suarez Nieto et al[17] and Becker et al[16] found a correlation in only 54% and 50% of their cases, respectively. These findings indicate that culture results from wound catheters do not reliably identify either the infecting pathogens or patients at high risk for infection.

Organisms recovered from infected wounds differ from those isolated from preoperative cultures.[16] Almost all infections are polymicrobial and include both aerobic and anaerobic organisms.[6,16-18] The isolates most frequently encountered are *S aureus* and streptococcal species, whereas the most common gram-negative anaerobic organisms are *B melaninogenicus* and *Fusobacterium nucleatum.*[14,19] *Bacteroides fragilis,* which may be resistant to penicillin, is not usually present in the oral flora and therefore is rarely isolated from infected wounds. Gram-negative aerobic organisms such as *Klebsiella, Pseudomonas,* and *Proteus* species also are frequently isolated from infected wounds.

The role of gram-negative aerobic organisms in the pathogenesis of head and neck wound infection is unclear. Theoretically, prophylaxis against these organisms should not be necessary. Several studies have examined this question. Piccart et al,[8] in a randomized prospective trial, compared clindamycin (which has excellent gram-positive aerobic and anaerobic coverage but no gram-negative aerobic activity) with a combination of clindamycin and netilmicin (the latter being an aminoglycoside antibiotic that provides gram-negative aerobic coverage). Wound infections developed in 6 (16%) of the 37 patients receiving clindamycin alone, compared to 4 (9%) of 43 who received both antibiotics. The difference was not significant, and the investigators concluded that gram-negative aerobic coverage may not be necessary.

Johnson et al[20] postulated that the isolation of gram-negative organisms from infected wounds is the result of contamination by nosocomial organisms indigenous to the hospital. To investigate this hypothesis in a double-blind randomized trial, 104 patients were given as prophylaxis either clindamycin 600 mg or a combination of clindamycin 600 mg and gentamicin 1.6 mg/kg. The antibiotics were administered intravenously 1 hour before operation and every 8 hours for a total of four doses. Overall, wound infections developed in 4 patients: 2 in each study arm. All patients had polymicrobial infections. Gram-negative aerobes were isolated from the wounds of 3 patients, 2 of whom had received the combination of gentamicin and clindamycin. The investigators concluded from this preliminary study that gram-negative aerobic organisms do not contribute significantly to the pathogenesis of postoperative wound infections. The therapeutic implication is that use of potentially toxic antibiotics such as aminoglycosides and the more expensive third-generation cephalosporins can be avoided.

To substantiate and expand on these findings, we have undertaken a double-blind study of 230 patients at the University of Texas M. D. Anderson Cancer Center. Subjects have been randomized to receive either clindamycin alone or ampicillin–sulbactam sodium. Ampicillin provides gram-negative aerobic coverage; the addition of sulbactam, a β-lactamase inhibitor, broadens the spectrum to include gram-positive aerobes and anaerobic organisms. The combination is attractive for prophylaxis, since it offers broad-spectrum coverage with no nephrotoxicity or ototoxicity. Study results are expected to be published later this year.

Time and Duration of Prophylaxis. The timing and duration of prophylactic antibiotic administration has been ascertained through animal studies and clinical trials. Antibiotics are most suppressive when administered before wound contamination occurs. In laboratory animals injected with live staphylococci, Burke[21] demonstrated that antibiotics must be administered within 3 hours of contamination to suppress the growth of microorganisms and are ineffective if administered after this decisive period. In clinical practice, the prophylactic "antibiotic window" closes if the patient does not receive antibiotics in a timely fashion. They are of no value in preventing wound infection if administered in the recovery room.

Theoretically, once a watertight mucosal closure is obtained and the wound is copiously irrigated, no further bacterial contamination should occur. Therefore, a short course of antibiotics should be as effective as a more prolonged course in preventing wound infections. Several studies have been conducted to evaluate the relationship between the duration of prophylaxis and the rate of infection. In a prospective study of 140 patients randomized to receive carbenicillin for either 1 day or 5 days, wound infections developed in 14% (10 of 72) and 10% (7 of 68) of patients, respectively ($p = .52$).[8] The authors concluded that more prolonged administration of antibiotics does not reduce the risk of infection. Fee et al[22] compared administration of moxalactam for 1 day and 2 days and found no difference in infection rate among 30 randomized patients. Johnson[10] reported on 56 patients randomized to receive clindamycin and gentamicin for either 1 day or 5 days. Infection developed in 1 patient in the 5-day arm of the study as opposed to 2 patients receiving 1 day of prophylaxis (see Table). The difference was not significant, and the author concluded that more prolonged prophylaxis was not warranted.

In another multi-institutional study,[23] 109 patients considered at high risk for postoperative wound infection because of the need for myocutaneous flap reconstruction were randomized to receive cefoperazone for 1 day or 5 days. Among the 53 subjects receiving prophylaxis for 1 day, the infection rate was 18.9% (10 patients), compared with 25% (14 patients) in those receiving prophylaxis for 5 days. The difference was not statistically significant.

Although these and other previous studies have not shown benefit for administration of prophylactic antibiotics beyond 24 hours, many involved small numbers of patients. Unless a great difference in efficacy exists between short duration and long duration of prophylaxis, the risk of incorrectly accepting the null hypothesis (type II error) is great.[24] A study with a larger number of patients would be necessary to establish whether more prolonged administration of antibiotics is beneficial. Evidence exists that despite a presumably watertight mucosal closure, persistent salivary soiling of a wound may occur. As expected, continued salivary contamination increases the risk of postoperative wound complications.[25,26] Whether more prolonged antibiotic administration would decrease the risk of infection in these patients is unknown.

CONCLUSION

The selection of antibiotics for prophylaxis is based on several factors. The agent should target gram-positive aerobic skin flora and oral anaerobic organisms. Whether gram-negative aerobic coverage should be provided is controversial, but this coverage does not appear to be mandatory or as important as targeting the other pathogens responsible for wound infections. The drug should be given parenterally in adequate doses before wound contamination occurs. Use of antibiotics beyond 24 to 48 hours postoperatively does not appear to decrease the risk of infection and increases the risk of superinfection with resistant organisms. A cost-competitive antibiotic should be selected, provided its efficacy is equal to that of a more expensive drug. Finally, ototoxic and nephrotoxic antibiotics should be avoided, since alternatives exist that have a similar spectrum of activity but lack these side effects.

Antibiotics alone, however, are not sufficient to prevent wound complications. Adherence to sound surgical principles and the use of delicate soft tissue technique will minimize the risk of wound sepsis. Also important are debridement of devitalized tissues, meticulous watertight mucosal closure, and copious irrigation to flush microorganisms from the wound before final closure.

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OTITIS MEDIA UPDATE: PATHOGENESIS AND TREATMENT

G. Scott Giebink, MD
Minneapolis, Minnesota

Otitis media primarily affects children, but can also lead to lifelong sequelae. Middle ear histopathologic changes and clinical manifestations can represent any part of a disease continuum, from acute to recurrent to chronic otitis media. Acute otitis media is most often caused by an acute respiratory viral infection and secondary replication of bacteria in the middle ear space and tissues, leading to symptoms and signs of infection (ie, fever, pain, tympanic membrane erythema). Antimicrobial therapy is the mainstay of management, and clinical response to different antimicrobial drugs appears to be similar. The bacteriologic efficacy of these drugs, however, is quite variable. Clearly, antimicrobial treatment of acute otitis media, which currently is largely empiric, must be fine-tuned on the basis of patient and disease variation.

KEY WORDS — antibiotics, bacterial infections, otitis media, viral infections.

INTRODUCTION

Otitis media (OM) is one of the common diseases of infants and young children, and its complications and sequelae often persist into the adult years. Recognition of this chronicity has led to changes over the last five decades in the management of OM in children. New therapeutic interventions have, in turn, generated management controversies. An understanding of the epidemiology and pathophysiology of OM provides the basis for evaluating these controversies and for developing new treatment and prevention strategies.

OTITIS MEDIA CONTINUUM

Epidemiologic studies performed in the last decade provided important clues to OM pathogenesis. Perhaps foremost among these are studies indicating that chronic otitis media with effusion (OME, called by some secretory otitis media) commonly follows acute otitis media (AOM), and that intractable chronic OM (with granulation tissue and damage to middle ear ossicles) usually follows recurrent AOM and chronic OME. These epidemiologic clues suggest that each of the various types of OM represents part of the continuum of a single disease process. Acute purulent OM is the disease form most clinically apparent, and there are transitions to chronic OME, including serous OM and mucoid OM. Eventually, some children experience chronic OM episodes with irreversible middle ear damage. Many OM episodes occurring during the first year of life are clinically asymptomatic, yet are as important as symptomatic episodes in predicting the likelihood of future middle ear disease.[1]

The OM continuum is illustrated by the overlap in types of effusion.[2] In AOM, purulent effusion predominates, but in about one in five cases an acute middle ear bacterial infection is superimposed on chronic mucoid effusion. In chronic OME, mucoid effusion predominates, but in one of three cases no effusion is found at myringotomy — yet the middle ear mechanics, reflected by tympanometric findings, are abnormal.

The results of prospective studies measuring the persistence of effusion after treatment confirm the existence of a disease continuum. In studies of randomly selected children with AOM, middle ear fluid had not cleared in 40% to 70% after 2 weeks (when treatment stopped). Twenty percent still had OME or abnormal middle ear function at 8 weeks, and few experienced clearance after that time. In a study that measured effusion disappearance in a group of children at high risk for chronic OME,[3] the disease persisted in 80% after 8 weeks. High-risk factors in this study — bilateral disease, day-care attendance, and effusion present for at least 4 weeks before the presenting AOM episode — were evaluated when each child initially presented with AOM. These studies illustrate that AOM, rather than being an uncomplicated, self-limiting disease in all children, becomes a chronic disorder for many.

The OM continuum is also manifest in middle ear fluid and the surrounding mucoperiosteal tissues. Response of these tissues to progressive middle ear disease leads to damage and local sequelae. Normal middle ear mucosa is composed of a single layer of squamous and cuboidal epithelial cells overlaying a thin subepithelial space. In serous OM, the epithelium is unchanged, but the subepithelial space is edematous. In purulent OM there are densely infiltrating cells that are acutely inflamed. The histopathology of mucoid OM is quite different; the epithelium is metaplastic, with secreting goblet cells, subepithelial edema, vascular dilatation, and few inflammatory cells. Several recent studies have documented the frequent occurrence of clinically silent progressive damage to middle ear tissue in the presence of chronic OME.[4] These findings indicate

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From the Departments of Pediatrics and Otolaryngology, University of Minnesota School of Medicine, Minneapolis, Minnesota.
REPRINTS — G. Scott Giebink, MD, Box 483 UMHC, 420 Delaware St SE, Minneapolis, MN 55455.

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the need for more sensitive methods of diagnosing progressive middle ear disease.

OTITIS MEDIA AND VIRAL INFECTION

Epidemiologic studies have shown a high degree of correlation between AOM and upper respiratory tract illness, the winter season, and day-care attendance. This suggests that respiratory viruses are important in the pathogenesis of OM. Because of the technical limitations of virus isolation, however, it has been difficult to document such a relationship. Recently, new laboratory methods have made possible the demonstration of viral antigens in middle ear effusion and nasopharyngeal secretions. In a study of 137 children with AOM, Sarkkinen et al[5] showed a temporal association between respiratory virus infections and pathogenic bacteria in acute middle ear effusion. Each case was analyzed according to whether a respiratory virus was isolated from middle ear fluid or the nasopharynx and whether pathogenic bacteria were cultured from the effusion. Among the study subjects, 19% had both a viral isolate and bacteria in the effusion, 36% had bacteria in the effusion without a viral isolate, 22% had a viral isolate without bacteria in the effusion, and 23% had sterile effusion and no viral isolate.

Some respiratory viruses are more closely associated with AOM than others. According to a study by Henderson et al,[6] these are respiratory syncytial viruses, adenoviruses, and influenza A and B viruses. These results suggest that certain viruses have unique effects on local systemic defenses that contribute to the development of OM. Studies of OM in children and in animal models have explored mechanisms of respiratory virus and bacterial interaction in pathogenesis. These have revealed a peak time during influenza A virus infection when susceptibility to bacterial OM is greatest; this peak susceptibility correlates with the time of maximum virus-induced damage to eustachian tube epithelium and with virus-induced reduction in blood polymorphonuclear leukocyte function (chemotaxis and intracellular killing).[7] Results of both clinical and basic research suggest that immunization to prevent respiratory virus infection might have a dramatic effect on the overall incidence of OM in children.

OTITIS MEDIA AND BACTERIAL INFECTION

Bacteriologic studies of middle ear effusion in AOM and chronic OME indicate that bacterial as well as viral immunoprophylaxis might be useful. There are at least two indications that the middle ear is protected by immune defenses, both local and systemic, that mature with age: bacteria causing AOM are cleared from the ear by specific antibodies, and the incidence of AOM decreases with age, suggesting that bacterial vaccination at a young age might prevent these infections.

Several studies were performed in the late 1970s to determine whether vaccination with pneumococcal polysaccharides would prevent pneumococcal OM. In a group of children 7 to 24 months of age, a 51% reduction in incidence of disease was seen with vaccination.[8] During the first 6 months after vaccination, there was also a 67% reduction in incidence of OM caused by the most immunogenic vaccine types. However, since only a few of the included types were immunogenic in this age group, there was only a small and insignificant effect on the overall rate of OM. The study demonstrates, nonetheless, that use early in life of a vaccine with broader immunogenic potential would be expected to have an appreciable effect on overall incidence of OM, since the pneumococcus is the principal bacterial middle ear pathogen.

Antimicrobial therapy of AOM is still the mainstay of management. Several drugs have been approved for this indication, including amoxicillin, amoxicillin–clavulanate potassium (Augmentin), cefaclor (Ceclor), erythromycin ethylsuccinate–sulfisoxazole acetyl (Pediazole), and trimethoprim-sulfamethoxazole (Bactrim, Septra). Cefuroxime axetil (Ceftin) and cefixime (Suprax) have been introduced recently, but large-scale clinical trials have not yet been conducted to ascertain whether their efficacy is comparable to that of the aforementioned drugs.

Most of the antimicrobial drugs approved by the Food and Drug Administration have approximately equal clinical efficacy in AOM, but recent studies have shown a striking delay in bacteria-killing effect for some agents. Although clinical outcomes usually have been similar in small-scale trials comparing results with various agents in the treatment of AOM, these recent studies indicate that clinical measurements often do not reflect differences in antimicrobial efficacy.

A trial comparing amoxicillin-clavulanate with cefaclor, for example, showed no difference in the rate of symptomatic improvement 3 to 6 days after the start of treatment.[9] However, the antibacterial efficacies of the two drugs were dramatically different: a 3% failure rate with amoxicillin-clavulanate and a 25% failure rate with cefaclor. These differences were apparent regardless of the initial pathogen, and differences in bacteriologic response rates could not be explained by patient noncompliance or bacterial resistance.

These clinical studies raise the question of whether impaired distribution of antimicrobial drugs into the middle ear and resulting subtherapeutic middle ear concentrations explain AOM bacteriologic treatment failures.[10] My colleagues and I have explored this question in the chinchilla model of OM and have preliminary evidence that distribution of antimicrobial drug into the middle ear varies widely among animals with the same clinical condition (ie, pneumococcal OM), and low concentrations are associated with persistence of the infection. Since the model closely parallels AOM in children, we suspect that there is also wide variation in middle ear antimicrobial concentrations in children with acute disease. These differences are probably magnified in children with chronic OME because of the wide variation in pathologic changes. It is therefore extremely important that new antimicrobials for treatment of AOM show bacteriologic as well as clinical efficacy.

For the clinician treating a child with AOM, prescribing should be done with knowledge of the possible variations in drug concentration in mind. Clinical failure after 3 to 5 days of antimicrobial treatment should not necessarily be assumed to indicate infection with a resistant organism; instead, it may suggest failure of the drug to reach effective concentrations in the middle ear. Aspiration of middle ear fluid, a simple office procedure, is important in bacteriologic assessment of children who fail to improve.

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ADENOIDECTOMY AND OTITIS MEDIA

GEORGE A. GATES, MD
HARLAN R. MUNTZ, MD   BRENDAN GAYLIS, MD
ST LOUIS, MISSOURI

Adenoid enlargement has traditionally been considered a factor in otitis media; adenoid size, however, does not appear to be correlated with otitis media occurrence. Presence of pathogenic bacteria in the adenoids of children with otitis media has been shown, and adenoidectomy appears to affect the middle ear primarily by removal of the source of infection in the nasopharynx. Three recent randomized, controlled studies showed the efficacy of adenoidectomy in the treatment of chronic secretory otitis media. In one study comparing no treatment, adenoidectomy, and adenotonsillectomy, a significant benefit was seen with adenoidectomy that was not enhanced by tonsillectomy. Another study that compared adenoidectomy, tympanostomy tubes, and a combination of the two showed a significant reduction in effusion time and less surgical retreatment over 2 years in the two adenoidectomy groups. The third study demonstrated the effect of adenoidectomy in children with recurrent chronic otitis media with effusion after failure of tympanostomy tube insertion. All three studies showed that the effect of adenoidectomy was independent of adenoid size. This review discusses current concepts of adenoid physiology and pathology, the major adenoidectomy studies, and indications for the procedure.

KEY WORDS — adenoidectomy, otitis media, tympanostomy tubes.

INTRODUCTION

Adenoidectomy is being reassessed because of new information validating its effectiveness in the treatment of children with otitis media.[1-3] Once the principal surgical treatment of otitis media prior to the widespread use of tympanostomy tubes, adenoidectomy has gradually been used less frequently in the United States, but not in other parts of the world.[4] Probable reasons for this change are longer operating time; risk of hemorrhage and other complications, such as hypernasality; lack of understanding of the procedure's effect (which is indirect) on the middle ear; and failure to demonstrate an improved outcome.[5-7]

Approximately 1 million children undergo surgical treatment for otitis media annually in the United States. Because of conflicting information about the efficacy of treatment of middle ear infections in general, and the role of adenoidectomy in particular, this paper reviews current concepts of the pathophysiology of the human adenoid, analyzes the major studies of the effectiveness of adenoidectomy, and develops a theoretic basis for the use of adenoidectomy in the treatment of otitis media.

The term otitis media is used herein to indicate any stage of otitis media with effusion. The qualifications acute, subacute, and chronic indicate specific stages. The terms chronic otitis media with effusion and secretory otitis media are used synonymously here. The use of adenoidectomy for airway obstruction, sleep apnea, chronic nasopharyngitis, or sinusitis is outside the scope of this discussion.

BACKGROUND

The adenoid, or pharyngeal tonsil, forms the superior, central part of the ring of lymphoid tissue surrounding the oropharyngeal isthmus, described by Wilhelm von Waldeyer (1836-1921).[8] Historically, the term adenoids was used to indicate enlargement of the pharyngeal tonsil. We use adenoid as a singular noun to indicate the pharyngeal tonsil regardless of its pathologic condition. The palatine (faucial) tonsils, the lingual tonsils, and numerous minor collections of lymphoid tissue are the other components of Waldeyer's ring, which in the aggregate are an important part of the gut-associated lymphoid tissue system. All the structures of Waldeyer's ring have similar histologic features and, presumably, similar function.

The adenoid is covered by a pseudostratified ciliated columnar epithelium rich in goblet cells, plicated to form numerous surface folds, which increase the total surface area. Abundant lymphocytes are found within, especially in the crests of the folds. The adenoid develops as a midline structure by the fusion of two lateral primordia that become visible during early fetal life,[9] is fully developed during the seventh month, and increases in size until the fifth year of life, often causing some degree of airway obstruction. Thereafter the adenoid gradually atrophies, the nasopharynx grows, and the airway improves.[10,11]

The adenoid is an important site of contact of inhaled microorganisms and other antigens with immunoreactive cells. The nasal mucociliary blanket carries material posteriorly across the adenoid. With the other components of Waldeyer's ring, the adenoid is important in the mucosal immunity of the upper aerodigestive tract. Like the palatine tonsil, the adenoid is a B-cell organ: B lymphocytes com-

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From the Department of Otolaryngology, Washington University School of Medicine, St Louis, Missouri.

REPRINTS — George A. Gates, MD, Dept of Otolaryngology, Washington University School of Medicine, Campus Box 8115, 517 S Euclid Ave, St Louis, MO 63110.

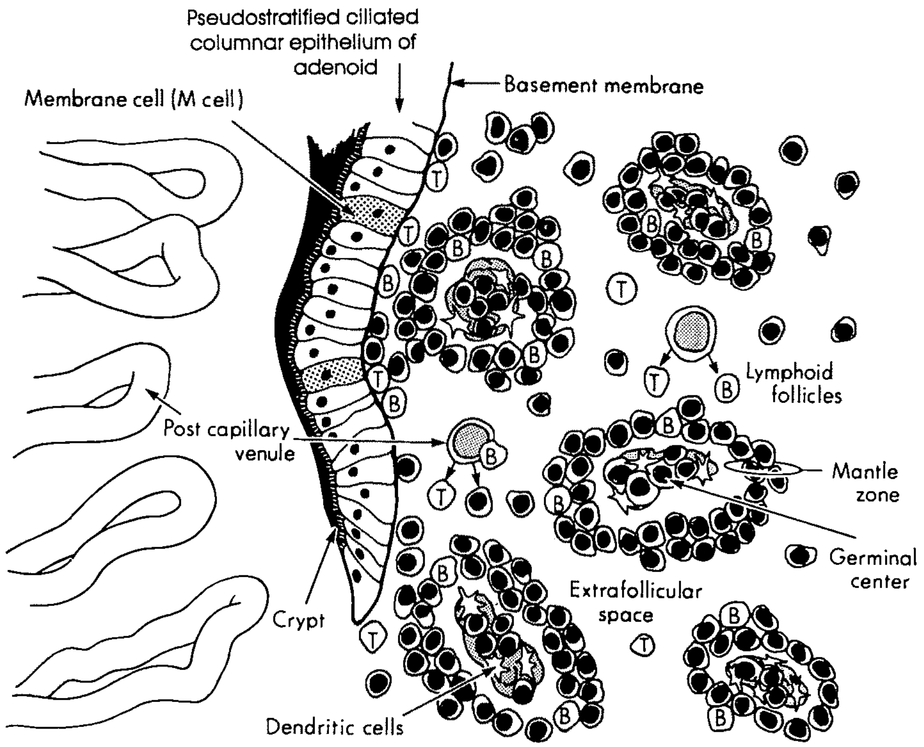

Fig 1. Functional immunologic structure of adenoid in relation to crypt and postcapillary venule. Several follicles with active germinal centers are shown, in which antigen-processing cells come into relationship with B cells. (Redrawn with permission from Richtsmeier and Shikhani.[13])

prise 50% to 65% of all adenoid lymphocytes; T lymphocytes, 40%; and mature plasma cells, 3%. In contrast, 70% of the lymphocytes in peripheral blood are T cells. The immunoreactive lymphoid cells of the adenoid are found in four distinct areas: 1) reticular cell epithelium, 2) extrafollicular area, 3) mantle zone of lymphoid follicle, and 4) germinal center of lymphoid follicle[12] (Fig 1[13]).

The reticular cell epithelium contains specialized membrane cells (M cells)[14] that transport antigens from the nasopharyngeal lumen. The extrafollicular area is populated mainly by T lymphocytes (T helper and T suppressor cells). Dendritic cells are also found in the extrafollicular area.

The lymphoid follicles consist predominantly of B lymphocytes in various stages of maturation. The centroblasts (the most immature B cells) are found at the base of the lymphoid follicle, whereas more differentiated cells such as the centrocytes, immunoblasts, and plasmacytoid cells are found in the mantle zone. Some T cells also appear among the B cells of the lymphoid follicles.

Once taken up by the M cells, antigens are transported inward through a tubovesicular system. The M cells facilitate antigen contact to lymphocytes through specialized antigen-presenting and antigen-processing cells that consist primarily of macrophages, dendritic cells, human leukocyte antigen (HLA)-DR-positive endothelial cells, and epithelial cells.[15] The antigens are presented to the T lymphocytes in the extrafollicular area. Recognition of these antigens by the T cells is thought to occur within the context of the major histocompatibility complex.[16] Although HLA-A, HLA-B, and HLA-C antigens are present on all nucleated cells, HLA-DR antigens are present only on specific immunocompetent cells such as B cells, macrophages, and activated T cells.

Once exposed to a particular antigen, T cells undergo blastogenesis and clonogenic proliferation. These T cells react with and stimulate B lymphocytes in the follicles. Blastogenesis of B cells is mediated by T helper and T suppressor cells,[17] but the exact mechanism is unknown. Adenoid T helper and T suppressor cells also produce interferon.[18]

Low antigenic signals stimulate the differentiation of B lymphocytes into immunoglobulin-producing plasma cells.[15] High-level antigenic stimuli result in clonal proliferation of B cells within the germinal centers. Some of these B cells migrate into the pharynx and other paraglandular structures to produce antibody, while a subset remain in the follicle as memory cells.

Immunoglobulins (Igs) produced by the adenoid include IgG, IgA, IgM, and IgD; there is a virtual absence of lymphocytes producing IgE.[13] Immunoglobulin G appears to pass into the nasopharyngeal lumen by passive diffusion (Fig 2[17]).

There are conflicting reports regarding the immunologic consequence of tonsillectomy and adenoidectomy, yet it is clear that no major systemic immunologic deficiencies result from these procedures.[19] Ogra[20] showed a threefold to fourfold drop in titers in children previously immunized with live poliovirus vaccine. In a study by D'Amelio et al,[21]

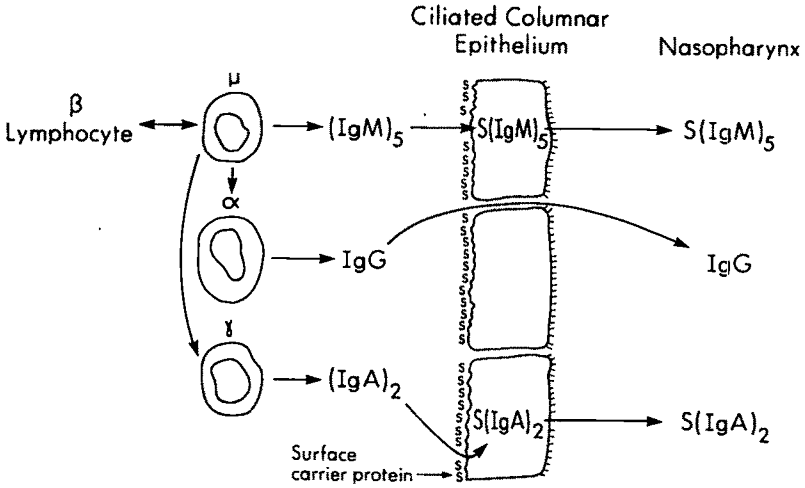

Fig 2. Antibody production in adenoid, as proposed by Brandtzaeg.[17] Migrating cells enter adenoid through postcapillary venule and produce IgM and IgA, which are actively secreted through epithelial cells into lumen. Intracellular leakage during inflammation increases amount of IgG, which is not actively secreted in adenoid because it lacks J chain, unlike IgM and IgA.

serum IgA levels in posttonsillectomy patients were lower than those in age-matched controls, but the functional significance is unclear. Because adenoidectomy alone does not disturb the remainder of Waldeyer's ring, the likelihood of a major immunologic sequela from adenoidectomy is remote.

The chief clinical adenoid disorder in children is enlargement, and its principal symptom is nasal obstruction or mouth breathing. Both acute and chronic adenoiditis occur, but little has been written about the clinical pathology of the adenoid because of its relative inaccessibility to physical examination or clinical testing.

Although adenoid and tonsil enlargement are often referred to clinically as hypertrophy, they are due to clonal expansion of the number of immunocompetent cells[22,23]; hyperplasia, rather than hypertrophy, is therefore the correct descriptor.

The principal stimulus for adenoid hyperplasia appears to be infectious. Brook[24] and DeDio et al[25] found elevated quantitative bacterial counts in adenoids removed for otitis media or for obstruction, whereas Pillsbury et al[26] demonstrated high counts only from children with recurrent acute otitis media, and not in adenoids removed for hyperplasia or serous otitis media. The latter group also found no correlation between adenoid size and the presence of infection. Thus, there is consistent evidence for the presence of pathogenic bacteria in the adenoids of children with otitis media, but conflicting evidence for the same phenomenon in those with symptomatic enlargement without otitis media.

Although hyperplasia is a physiologic response to antigen exposure, chronic infection may actually cause cellular depletion.[22] Brandtzaeg et al[18] demonstrated a general decline in immunocytes, except for IgD-producing cells, in all compartments in the tonsils of patients with recurrent tonsillitis. In addition, they noted increased fibrosis in the extrafollicular area, which also suggests a decline in immunoreactivity. Thus, the available evidence suggests that adenoid enlargement, a common phenomenon in the 4- to 7-year-old age group,[11] does not necessarily indicate abnormality, and that chronic infection may result in a decrease in size.

PATHOPHYSIOLOGY IN RELATION TO OTITIS MEDIA

OTITIS MEDIA

Otitis media in children may be acute, with signs and symptoms of inflammation and an effusion, or chronic, as indicated by an indolent, persisting middle ear effusion that may be purulent, mucoid, or serous. Acute otitis media is more common in the first 3 years of life, and chronic otitis media is more common from 4 years onward. However, since they are two stages of the same disease, either form may appear at any age. The same types of pathogenic bacteria are found in both acute and chronic effusions, although with greater prevalence in the former.

Because most cases of acute otitis media are bacterial, any theory of pathogenesis must account for how the bacteria reach the middle ear. It is generally recognized that otitis media begins in the nose, ie, that viral nasal infection precedes the ear infection.[27] Pathogenic bacteria appear subsequently and are found in the nasopharynx in 97% of patients with acute otitis media, with organisms corresponding to those isolated from middle ear effusion in 69%.[28] The adenoids of children with recurrent acute otitis media contain pathogenic bacteria in clinically significant amounts.[24-26]

It is logical to postulate that nasopharyngeal microorganisms enter the middle ear via the eustachian tube, possibly facilitated by nose-blowing or closed-nose swallowing (Toynbee maneuver).[29] Alternatively, the organisms may be aspirated into the middle ear as a result of negative middle ear pressure generated by sniffing.[30] This phenomenon is termed eustachian tube reflux and has been demonstrated radiographically in children with otitis media.[31] Its prevalence is unknown because of the lack of a widely available noninvasive method of detection.

For didactic purposes, we identify two broad categories of chronic otitis media with effusion: persistence of an acute effusion and secretory otitis media. However, it is not possible to distinguish them on clinical grounds unless the patient has been followed closely prior to onset. In younger children, chronic effusion appears to be the unresolved stage of an acute otitis media in which middle ear clearance is delayed. Teele et al[32] found persistent effusion (>30 days) in 40% of children following their first episode of acute otitis media, with continued effusion in 10% for up to 3 months. Putative mechanisms for the failure of middle ear clearance include ciliary dysfunction, mucosal edema and hyperplasia, viscosity of secretions, and a middle ear–nasopharyngeal pressure gradient.

Many cases of chronic effusion, especially in older children, occur without clinically evident antecedent acute otitis media, although most patients have had otitis media in earlier childhood. Therefore, it is necessary to postulate a second mechanism. In these cases, secretion of fluid by the abnormal middle ear mucosa (ie, secretory otitis media) is thought to be the origin.[33] Antigenic stimulation in an ear sensitized by prior infection may result in recurrent effusion in the absence of clinically identifiable acute infection. It would thus appear that in these cases the fluid is produced by the middle ear mucosa in response to subclinical antigenic stimulation rather than by an overt acute inflammatory process. Many investigations have confirmed the finding of Senturia et al[34] that chronic middle ear effusion is not sterile, as previously hypothesized, and that it contains the same spectrum of microorganisms as is found in acute effusions. The available evidence thus links chronic middle ear effusion, regardless of its clinical presentation, to bacterial infection.

RELATIONSHIP OF ADENOID AND OTITIS MEDIA

The enlarged adenoid has long been implicated as a factor in the genesis of otitis media,[35] but the pathophysiology of this relationship has not been rigorously examined. Three mechanisms are generally postulated: the adenoid 1) causes eustachian tube obstruction, 2) promotes eustachian tube reflux, and 3) is a source of pathogenic bacteria. Because eustachian tube dysfunction is found in virtually all patients with otitis media in whom testing has been performed,[31] and because the adenoid is situated so near the mouth of the eustachian tube, a cause-and-effect relationship between the adenoid and eustachian tube dysfunction has long been presumed.

Under our working hypothesis that bacteria from the adenoid and nasopharynx enter the middle ear via the eustachian tube, it is unnecessary to postulate that eustachian tube obstruction must precede acute otitis media, as has been held since the time of Politzer.[36] Indeed, in the early stages of an infection, bulging of the tympanic membrance and positive middle ear pressure are often seen. Furthermore, it has never been shown that the adenoid physically obstructs the eustachian tube. Studies of the eustachian tube in children with chronic otitis media indicate that anatomic or mechanical obstruction of the tube is less common than functional obstruction[31]; if the adenoid were mechanically obstructing the tube, one would expect just the opposite. The site of eustachian tube obstruction in 10 adult patients with chronic otitis media with effusion was localized with a thin pressure catheter to the distal part of the cartilaginous portion, 5 to 15 mm from the orifice, rather than in the orifice proper.[37] Thus, the role of eustachian tube obstruction in acute otitis media is called into question, and the locus of obstruction, when it occurs, is more likely to be within the eustachian tube than at its nasopharyngeal ostium.

Sade[33] was one of the first to discuss the open eustachian tube and the role of infection in otitis media. During swallowing, nasopharyngeal pressure rises and material in the nasopharynx may enter the eustachian tube and pass back into the middle ear. A large adenoid elevated by the soft palate during swallowing could obstruct the choanae and contribute directly to increased nasopharyngeal pressure and thus indirectly to reflux. Children with patulous eustachian tubes, in whom free flow of radiographic material into the middle ear occurs, have been shown to be at high risk for otitis media.[31] That young children have shorter, straighter, and more compliant eustachian tubes than adults has been recognized as an important factor in the pathogenesis of otitis media in children.[38]

If reflux were the consequence of adenoid enlargement, there would be a greater prevalence of such enlargement in children with otitis media. Studies have shown no difference in adenoid size, either radiographically[39] or by weight,[40] in children with otitis media compared with control children. No difference was noted in the recurrence rate of effusion in children with large versus small adenoids, nor was the effect of adenoidectomy dependent on adenoid size.[1-3] Thus, the evidence does not support the classic theory that adenoid enlargement is a factor in the pathogenesis of otitis media. It appears to us that adenoidectomy affects the middle ear primarily by removal of a source of infection in the nasopharynx, rather than by any direct or indirect effect on the eustachian tube, and that the beneficial effect of adenoidectomy is independent of adenoid size.

ADENOIDECTOMY

Historically, adenoidectomy for otitis media has been justified by one or more reasons: relief of airway obstruction to decrease eustachian tube reflux, improvement in eustachian tube function, and elimination of a source of chronic nasopharyngeal infection. Because of the lack of efficient clinical methods to determine independently which factor may be relevant in a specific case, the incidence of these three indications is unknown. It is likely that more than one factor may apply in any given case. Because the operative procedure is the same regardless of the rationale for performing it, this subject has not received great attention in the literature.

EFFICACY

Existing studies of the efficacy of adenoidectomy have yielded conflicting results. The wide variation in experimental design and methods makes direct comparisons of efficacy difficult. Important variations include sample size, observer validation, entry criteria, randomization strategies, and follow-up procedures. The principal studies cited as showing a lack of effect of adenoidectomy are those by Roydhouse,[5] Fiellau-Nikolajsen et al,[6] and Widemar et al.[7] In these studies, comparisons of outcome were made at one or a few widely spaced observation times rather than sequentially at regular intervals; this schedule prevented observation of recurrent interval disease. Thus, it is likely that these studies were not sensitive enough to detect differences among the treatment groups that might have been clinically significant. Studies demonstrating a significant effect from adenoidectomy are those by Maw,[1] Gates et al,[2] and Paradise et al.[3] Other, older studies of adenoidectomy[41-43] are not reviewed here because of severe flaws in experimental design.[44]

Studies Failing to Demonstrate Efficacy. In the study by Roydhouse,[5] 100 children 3 to 14 years of age who had failed medical therapy were assigned to receive tympanostomy tubes with or without adenoidectomy. Otoscopy, the sole measure of outcome, was performed annually, and although there was a slightly higher disease-free rate in the adenoidectomy group (82% versus 77% at 1 year, 85% versus 82% at 2 years, and 94% versus 84% at 3 years), he concluded that adenoidectomy was not effective. The principal limitations of this study are reliance on nonvalidated otoscopy as the sole outcome measure; the lack of interval otoscopy, so that the condition of the ears could be assessed only once a year; and the unequal number of unilateral cases, with more in the tympanostomy tube–only group, which biased the results against adenoidectomy. Statistical analysis of the differences in outcome was not done, nor was the likelihood of type I or type II errors calculated.

Over a 4-year period, Fiellau-Nikolajsen et al[6] observed 42 3-year-old children who had been randomly assigned to receive bilateral myringotomy with or without adenoidectomy. No significant difference in outcome at any assessment interval was noted, even though the children who had undergone adenoidectomy did better generally. In this study nearly half of the children had normal tympanograms (type A or C1) preoperatively, in contrast to most other studies, in which care was taken to include only study subjects with effusion. Thus, the inclusion of a large proportion of cases in which the outcome was destined to be good regardless of therapy may have decreased an already small sample size to the point that a clinically significant difference could not have been detected. Probability of a type II error was not calculated.

Widemar et al[7] nonrandomly assigned 54 children with mucoid effusion, selected from 78 with chronic otitis media undergoing myringotomy, to receive or not receive adenoidectomy. Outcome was reported only at the second anniversary of the procedure, at which time otoscopic findings were normal in 13 (54%) of 24 children who had adenoidectomy versus 13 (37%) of 35 children who had not had adenoidectomy. They found this difference not statistically significant, but acknowledged that their limited sample size would not allow detection of a difference of 30% or less between the groups. The study was flawed by the unequal size of the groups and biased against adenoidectomy by the greater number of bilateral cases in the adenoidectomy group (15 [63%] of 24) versus the nonadenoidectomy group (18 [51%] of 35).

Studies Demonstrating Efficacy. Maw[1] studied 103 children, 2 to 12 years old (mean age, 5.25 years), with bilateral chronic otitis media with effusion whose condition was resistant to 12 weeks of antihistamine treatment. He randomly assigned them to three groups: adenotonsillectomy (n = 34), adenoidectomy (n = 36), or neither (n = 33). At operation, one ear was randomly assigned to receive a tympanostomy tube. Clearance of effusion in the unoperated ear (as judged by otoscopy) was the criterion of success. At 3, 6, 9, and 12 months after operation, the clearance rates were, respectively, adenoidectomy 56%, 64%, 58%, and 72%; adenotonsillectomy 50%, 59%, 62%, and 62%; and control 22%, 26%, 19%, and 26%. The difference between the two surgical groups and the control group at 12 months (71% versus 26%) was highly significant, but the difference between the adenoidectomy and the adenotonsillectomy groups was not. The lack of tympanometric corroboration of the otoscopic findings is a weakness of this study.

Gates et al[2] randomly assigned 491 children, 4 to 9 years old, with secretory otitis media persisting 60 days or more after repeated medical therapy to surgical control (n = 107), tympanostomy tubes (n = 129), adenoidectomy (n = 130), or adenoidectomy plus tympanostomy tubes (n = 125). Antimicrobial therapy had failed for all children, and none had had prior tonsil or adenoid surgery. Bilateral myringotomy and suction aspiration of the middle ear were performed in all cases. The fossae of Rosenmüller were not curetted. The children in the two adenoidectomy groups had significantly less time with effusion and fewer repeat surgical treatments over the 2-year follow-up period than those who did not have adenoidectomy at each level of tympanostomy tube use. There was no difference in the time with abnormal hearing in the three surgical groups, whether or not tympanostomy tubes were used. The reduction in morbidity (from control levels) in time spent with recurrent effusion was 29% with tympanostomy tubes only, 38% with adenoidectomy and myringotomy, and 47% with adenoidectomy and tympanostomy tubes. Although two thirds of the children were Mexican-American, and thus there might be a question of generalizability, their outcomes did not differ from those of the rest of the children.

Paradise et al[3] examined the effect of adenoidectomy in two groups of children with chronic otitis media with effusion recurring after tympanostomy tube treatment. One group (n = 99) was randomly assigned, and in the other (n = 114), parental preference was used to determine whether adenoidectomy was performed. In both groups, the outcomes of the children who had undergone adenoidectomy were statistically better than those of the control children for both follow-up years, with greater differences in the first than the second year. Adenoidectomy included routine curettage of the fossae of Rosenmüller. In addition to significant reduction in time with effusion, clinically significant reductions in suppurative otitis media (28% and 35% in years 1 and 2, respectively) were noted; the difference was statistically significant only for the second year.

Study Conclusions. There is an important difference between clinical trials that fail to demonstrate an effect and those that demonstrate a lack of effect. The three studies cited above that failed to demonstrate an effect of adenoidectomy have not been convincing because their sample sizes were too small to avoid a large type II error and because the infrequency of outcome assessment could have prevented detection of clinically important differences.

The three more recent clinical trials, which had adequate sample size and frequent postoperative follow-up, demonstrated statistically significant and clinically important effects from adenoidectomy in reducing morbidity in children with chronic otitis media with effusion. Thus, the evidence supports the conclusion that adenoidectomy does modify the natural history of chronic secretory otitis media in severely affected children 4 years of age and older. However, a decision to use adenoidectomy in children in whom other forms of therapy have failed must take into account whether the magnitude of the effect is great enough to be clinically significant.

INDICATIONS

Evidence of efficacy is a necessary but not sufficient condition for establishing the indications for a surgical procedure. In deciding whether to recommend adenoidectomy, other factors should be considered. Adenoid size, however, does not appear to be one of them.[1-3] Assuming that there are no contraindications to surgery (blood dyscrasia, intolerance to anesthetic agents, etc) and that a submucous cleft of the palate has been excluded, the risks and costs of the operation must be balanced against its benefits. Tonsillectomy does not appear to offer any effect on middle ear effusion beyond that of adenoidectomy alone.[1]

Controversy exists regarding when a given child is a surgical candidate. The debate centers primarily on duration of effusion and whether persistent effusion, with its attendant mild conductive hearing loss, is harmful to the child's development. Space does not permit a detailed review of these yet-unsettled issues. We believe that even mild conductive hearing loss is a risk factor for impaired development, but that this risk may be reduced, to an unknown degree, by compensatory measures instituted by parents, teachers, and the children themselves.

After a decision is made to treat the child surgically, a second decision regarding tube insertion versus adenoidectomy with or without tube insertion is necessary. Arguments have been advanced that because it is simpler and less expensive, insertion of tympanostomy tubes should be used initially, with adenoidectomy reserved for recurrent cases.[45] However, owing to the substantially higher rate of reoperation after use of tubes only, the greater initial expense of adenoidectomy may be offset by the cost of repeat intubation procedures and the overall cost may be equivalent,[46] depending on hospital and physician charges. In making such a decision, risks versus effectiveness must be considered in light of the needs of the child and family.

We recommend surgical removal of the middle ear effusion, adenoidectomy, and, in most instances, tympanostomy tube placement for children with effusion and hearing loss persisting more than 90 days despite adequate antimicrobial therapy. In selected cases, tubes may be omitted as long as myringotomy and aspiration of the middle ear are performed.[2] Others advise waiting 120 days or more, knowing that the effusion may resolve with time. However, A. R. Maw (personal communication, 1988) has noted persistent effusion for up to 3 years in 40% of cases and up to 5 years in 25%. Thus, a balance must be reached between the probability of spontaneous resolution and the sequelae of prolonged morbidity with the risk of intercurrent infection. The time criterion is tempered by season: in the fall we are more likely to recommend surgery because of the high likelihood of exacerbation of the condition during the winter months; whereas in the spring, when otitis media and upper respiratory tract infections are less prevalent, spontaneous resolution of effusion is more likely and longer observation is warranted.

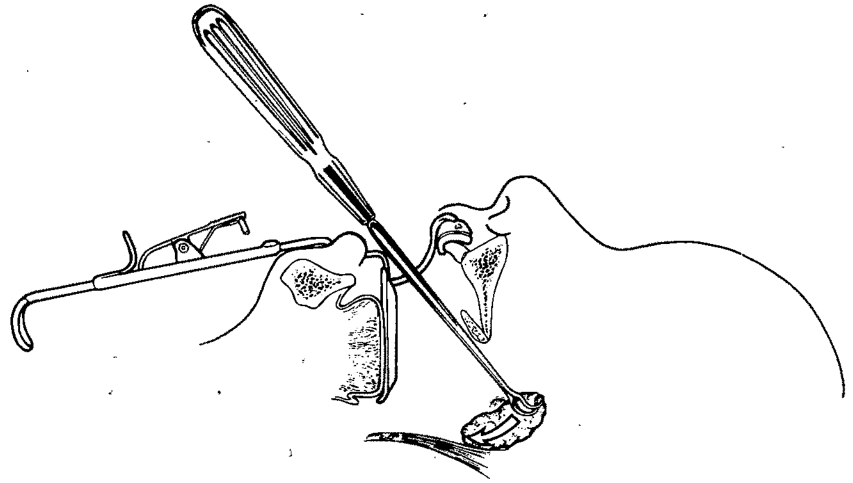

Fig 3. Adenoid removal. Adenoid curette is placed transorally. Patient is in Rose's position, with head and neck extended. Surgeon is seated at head of table.

SURGICAL CONSIDERATIONS

TECHNIQUE

Adenoidectomy is performed with the patient under general anesthesia and the airway assured by endotracheal intubation. The soft palate is retracted with a catheter. The adenoid is excised with curved curettes of various sizes and shapes by using a large mirror and either a headlight or the operating microscope to inspect the nasopharynx to assure completeness of removal (Fig 3). Curved biting forceps are useful to remove tissue not accessible by the curette. Bleeding usually stops promptly; pressure applied for a few minutes via sponges in the nasopharynx appears to assist the process, as does irrigation with saline at room temperature. Suction electrocautery permits precise coagulation of bleeding vessels and avoids the risk of stenosis from indiscriminate field cauterization (Fig 4). The procedure takes less than 15 minutes in experienced hands.

The goal of surgery is complete removal of the midline adenoid pad in order to achieve smooth reepithelialization of the nasopharynx. Curettage of the tissue in the fossa of Rosenmüller is done by those who strive for complete removal of all upper pharyngeal tissue, but not by others (ourselves included) for fear of scar tissue formation and contracture that might contribute to eustachian tube reflux. In either case, care must be taken to avoid direct injury to the eustachian tube that might result in stenosis.

Unlike its companion operation, tonsillectomy, adenoidectomy causes few postoperative symptoms. Mild ear pain is common but difficult to attribute to the adenoidectomy, because the majority of procedures are performed in conjunction with a procedure on the tympanic membrane. The child is able to eat normally as soon as nausea from the anesthetic has subsided.

COMPLICATIONS

The most common complication of adenoidectomy is postoperative bleeding. However, the incidence is low: only 1 of 250 procedures, performed by 13 surgeons, required operative treatment for bleeding, and none of the patients needed or received blood transfusion.[2] Helmus et al[47] noted that only 4 patients in 1,000 (0.4%) bled after outpatient adenoidectomy; all instances of bleeding occurred in the first 6 postoperative hours and were managed without transfusion.

Other, less common complications include nasopharyngeal stenosis and velopharyngeal incompetence (VPI). Stenosis results from excessive tissue destruction such as might occur from excessive use

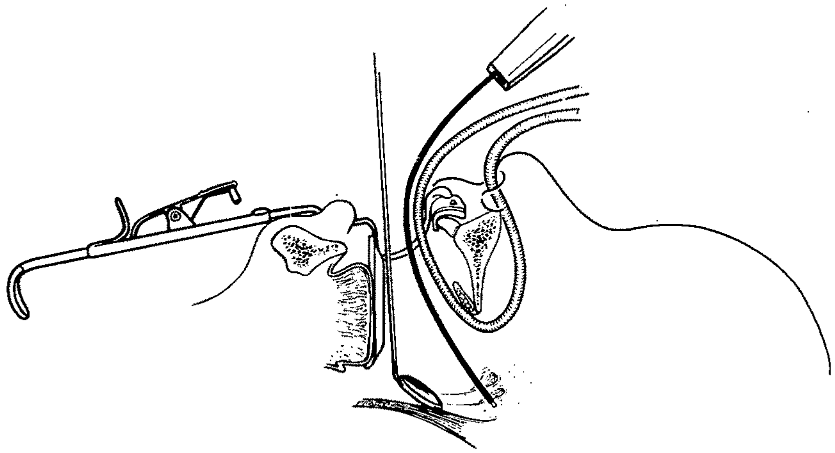

Fig 4. Soft palate, retracted with catheter, and curved suction cannula in place. Mirror control is used to achieve pinpoint hemostasis.

of electrocautery, excessive curettage of the fossae of Rosenmüller, and removal of the lateral pharyngeal bands.[48] Transient VPI may occur after removal of a large adenoid, but resolves quickly in the majority of cases. Persistent VPI is the most feared complication, since it requires either a prosthesis or a secondary procedure (pharyngeal flap) for correction. It is postulated that the majority of such cases are due to an undetected submucous cleft palate. Preoperative evaluation with fiberoptic nasopharyngoscopy is useful in detecting an occult posterior submucous cleft.[49]

To determine the safety of adenoidectomy in young children, we reviewed retrospectively the medical records of 63 children, 3 years or younger, who had undergone adenoidectomy consecutively at St Louis Children's Hospital. The indications for the procedure were obstructive sleep apnea (38%), recurrent acute otitis media (35%), chronic otitis media with effusion (29%), and sinusitis (22%). Some children had more than one indication. There were no intraoperative problems, and the average blood loss was 23 mL (range, <5 to 100 mL). Intraoperative suction cautery of nasopharyngeal bleeding sites was done routinely. None of the children required transfusion. There were no instances of postoperative hemorrhage. Most of the procedures were done on an outpatient basis. There were no cases of VPI or stenosis.

TYMPANOSTOMY TUBES

Space does not permit a detailed discussion here of the role of tympanostomy tubes in the treatment of otitis media in children. The gold standard for surgical treatment is insertion of tympanostomy tubes.[50] Their use has resulted in improved hearing and decreased recurrence of otitis media in large numbers of cases. However, the complications of tympanostomy tubes (purulent otorrhea, permanent perforation, recurrent effusion) are not clinically insignificant. Thus, the search continues for the most effective treatment strategy for children with otitis media. It is clear to us that neither the use of tympanostomy tubes nor adenoidectomy is the sole answer, and that continued study is needed to determine the ideal approach.

SUMMARY

Chronic bacterial infection of the adenoid is common in children with otitis media, and appears to be an important part of its pathogenesis. Removal of the adenoid hastens resolution of otitis media and decreases the incidence of recurrence in comparison to control groups. Nonetheless, otitis media does recur after adenoidectomy. The procedure thus cannot be considered curative, although it does significantly reduce morbidity.

Adenoidectomy is a relatively safe and effective minor operative procedure in trained hands. Nonetheless, its use should be evaluated in light of potential adverse consequences. Adenoidectomy should be considered in the primary surgical treatment of older children (≥4 years) with chronic secretory otitis media with effusion when medical therapy has failed and prolonged observation confirms the persistence of effusion and hearing loss. The role of adenoidectomy in younger children is still under study. The effectiveness of adenoidectomy in prevention of recurrent acute otitis media has not been established.

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ANTIMICROBIAL PROPHYLAXIS FOR RECURRENT ACUTE OTITIS MEDIA

JACK L. PARADISE, MD
PITTSBURGH, PENNSYLVANIA

Antimicrobial prophylaxis for recurrent otitis media was first reported in 1960 in an uncontrolled study using a long-acting sulfonamide in Native American children younger than 11 years of age. In subsequent controlled studies using various antimicrobial drugs (primarily aminopenicillins or sulfonamides) subjects receiving prophylaxis continued to have episodes of acute otitis media, but at rates substantially lower than those of controls. More recently, prophylaxis has appeared effective in reducing the number of acute recurrences, but not the cumulative proportion of time with middle ear effusion that was present independent of such recurrences. Although questions remain about choice of drug, optimal dosage schedules, risk of untoward drug reactions, duration of use, and the risk of encouraging the emergence of resistant strains of pathogenic bacteria, antimicrobial prophylaxis currently appears to be the most logical first approach in the management of the child with recurrent otitis media.

KEY WORDS — antimicrobial prophylaxis, recurrent acute otitis media.

The purpose of this paper is to review the use of subtherapeutic doses of antimicrobial drugs to prevent recurrences of acute suppurative otitis media (AOM), to summarize current knowledge about otitis prophylaxis, and to offer recommendations concerning its use.

RATIONALE FOR PREVENTION

In the child subject to repeated attacks of AOM, efforts at prevention seem justified for a number of reasons. Perhaps the most obvious is prevention of discomfort: both local discomfort as a direct result of middle ear inflammation, and general discomfort as a consequence of the febrile response to acute infection. Averting the usual accompanying conductive hearing loss is another consideration, even though the hearing loss often is inapparent or mild, and usually seems not to cause distress in the child. Prevention can also spare parents the cost of physician visits and drug therapy, of time lost from work, and, in extreme cases, of surgical procedures. Allaying parental anxiety and maintaining normal activities for both parent and child are two more good reasons. Last is avoidance of possible long-range sequelae of either otitis media or eventual surgical measures. These potential sequelae consist of structural middle ear damage and hearing loss and, much more arguably, short- or long-term impairment of speech, language, cognitive, or psychosocial development.[1,2]

METHODS OF PREVENTION

Approaches to the prevention of recurrent AOM include, in addition to antimicrobial prophylaxis, a variety of other interventions, discussion of which is beyond the scope of this review. These interventions consist of the administration of polyvalent pneumococcal vaccine, and the performance of myringotomy with or without tympanostomy tube placement and of adenoidectomy with or without tonsillectomy, either singly or as combined procedures. None of these, in my judgment, is as reasonable a first-try approach as antimicrobial prophylaxis.

ANTIMICROBIAL PROPHYLAXIS IN PERSPECTIVE

Short- or long-term antimicrobial prophylaxis is a well-established procedure under a number of circumstances: for the prevention of neonatal gonococcal ophthalmia; for the prevention of bacterial endocarditis in persons with congenital or rheumatic valvular heart disease; for the prevention, after appropriate exposure, of such varied infections as tuberculosis, syphilis, gonorrhea, diphtheria, pertussis, meningococcal sepsis or meningitis, and *Hemophilus influenzae* type b disease; for the prevention of traveler's diarrhea; in patients who have sickle cell disease or have undergone splenectomy; in patients with recurrent urinary tract infection; and in patients who have incurred burns, bites, or other contaminated injuries.

In most of these circumstances, however, the objective is protection against infection by a single bacterial organism, rather than by a variety of potential organisms, as is the case in AOM. Thus, it may not be reasonable to expect as satisfactory results from otitis media prophylaxis as from prophylaxis for one of these other conditions. Expectations about the efficacy of prophylaxis for recurrent AOM might be further tempered by the findings of studies in which prophylaxis was apparently not efficacious in preventing bacterial complications of measles and of viral upper and lower respiratory tract infections,[3] although it should be noted that comparable trials apparently have not been carried

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From the Ambulatory Care Center and Department of Pediatrics, Children's Hospital of Pittsburgh, and the Department of Pediatrics of the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

REPRINTS — Jack L. Paradise, MD, Children's Hospital of Pittsburgh, One Children's Place, Pittsburgh, PA 15213-3417.

out during the past two decades, during which time broader-spectrum antibacterial drugs have become available.

Potential complications of long-term prophylaxis include development of adverse drug reactions, emergence of resistant strains of bacteria, and suppression of symptoms or signs of acute infection rather than the infection itself, which could reduce the likelihood that the illness would be detected.

STUDIES OF PROPHYLAXIS FOR OTITIS MEDIA

The first reported study of antimicrobial prophylaxis for otitis media was conducted more than 30 years ago in Montana by Ensign et al.[4] The subjects were 120 Native American children less than 11 years of age, 91 of whom had a history of otorrhea during previous years. Sulfamethoxypyridazine, a long-acting sulfonamide no longer in use, was prescribed for all of the children, to be given in a single dose three times weekly to those weighing more than 9 kg (20 lb) and twice weekly to those weighing less. There was no prospective monitoring for either medication compliance or the occurrence of otitis media, but parents were later asked about both of these outcomes and the children were classified accordingly. Among children both with and without a history of otorrhea, earache and/or otorrhea reportedly occurred much less often in those who had received the drug regularly or irregularly than in those who had received it for only short periods or not at all. Although this study had major limitations in that it was uncontrolled and outcomes were based on parental account rather than direct observation, the degree of apparent benefit from prophylaxis was large enough to suggest that the benefit was real.

About a decade later, Maynard et al[5] studied the efficacy of ampicillin prophylaxis in 364 Western Alaskan Eskimo infants and children less than 7 years of age, most of whom had demonstrable tympanic membrane abnormalities. The children were divided into two groups matched for family size, age, sex, and history of otitis media. In double-blind fashion, subjects in one group received ampicillin (250 mg once daily if 2½ years of age or older; 125 mg once daily if less than 2½ years). The other group received placebo. An episode of otitis media was defined as the occurrence of otorrhea as reported by parents after an apparently otorrhea-free interval of at least 2 weeks. Subjects were studied over the course of 1 year. In the ampicillin-treated group, 24% developed one or more episodes of otorrhea and 4% developed three or more episodes, as compared with 40% and 11%, respectively, in the placebo group. These differences were statistically significant, and provided substantial evidence that ampicillin prophylaxis had been effective.

Even more persuasive results were reported by Perrin et al[6] in 1974. The subjects were 54 children, 11 months to 8 years of age, who were enrolled in a private practice in Rochester, NY, and who had histories of three or more episodes of AOM in the preceding 18 months or five or more episodes in the course of their lifetimes. They were studied over a 6-month period from December through May, a period chosen because AOM is more likely to occur then than in summer or fall. Subjects were assigned in a double-blind, crossover design; half received sulfisoxazole 0.5 g twice daily during the first 3 months of the study and placebo during the second 3 months, while the other half received the two medications in reverse order. The children were examined every 6 weeks, and the outcome measure was the number of AOM episodes. Criteria for this diagnosis were not specified. Of the 54 subjects, 4 developed one or more episodes while receiving sulfisoxazole, whereas 21 developed one or more episodes while receiving placebo. The difference was statistically significant ($p < .02$), as was the difference in attack rates: 0.15 episodes per child per 6 months in children receiving sulfisoxazole versus 1.05 in those receiving placebo ($p < .001$). The reduction in attack rate was not statistically significant in the subjects 6 years of age or older, perhaps because, as the authors suggested, the dose of sulfisoxazole had not been high enough.

These early studies of otitis media prophylaxis, as well as later studies of various designs with generally similar results,[7-15] have had a number of limitations in common. First, study design in most cases would not have permitted detection of nonsymptomatic episodes of AOM, even though such episodes occur frequently, especially in infants. Second, none of the studies provided unambiguous results concerning possible effects of prophylaxis on the occurrence of nonsuppurative (secretory) otitis media. Third, follow-up did not extend beyond 1 year, and in most studies was considerably shorter. And finally, none of the studies compared the efficacy of one antimicrobial drug with that of another.

Some of these issues have recently been addressed in a study conducted in Milan, Italy, by Principi et al,[16] of 96 children, 9 months to 5 years of age, each of whom had had three or more well-documented episodes of AOM in the preceding 6 months. At the time of entry into the study, 97% of the subjects still had either unilateral or bilateral middle ear effusion. The subjects were randomly assigned to receive either amoxicillin, trimethoprim-sulfamethoxazole (TMP-SMX), or placebo. Treatment was continued for 6 months, during which the subjects were examined at intervals of 4 to 6 weeks. In the course of follow-up, 9 of the 33 subjects in the amoxicillin group developed 11 episodes of AOM; 9 of the 33 subjects in the TMP-SMX group developed 9 episodes; and 19 of the 30 subjects in the placebo group developed 25 episodes. In each case the difference in outcome between the drug-treated and placebo-treated groups was statistically significant ($p<.01$).

The investigators also estimated the cumulative proportions of time with middle ear effusion for each of the three treatment groups. Overall, effusion was present 75.2% of the time in the placebo group, as compared with 67.8% and 64.2%, respectively, in the amoxicillin and TMP-SMX groups. However, among subjects who developed no episodes of AOM in the course of the study, little difference was found between the three treatment groups in the percent of time with effusion. The authors concluded that drug treatment, in reducing the number of AOM episodes, had correspondingly reduced the periods of effusion that accompanied and followed those episodes, but had not reduced the duration of effusion that occurred independent of AOM episodes.

In summary, the Milan study confirmed the efficacy of antimicrobial prophylaxis for recurrent AOM. The study showed no difference in efficacy between amoxicillin and TMP-SMX, but because of the small number of subjects, even a substantial difference might not have been detected. The study showed no effect of prophylaxis on the occurrence of middle ear effusion other than that attributable to AOM, but because virtually all of these subjects had had effusion at entry, these findings cannot be generalized to children who are effusion-free at the time prophylaxis is instituted.

CAUTION CONCERNING SULFONAMIDES

Because the Milan study, as well as earlier studies,[4,6-11,13,14] supports the use of a sulfonamide for AOM prophylaxis, two notes of caution are in order. First, the use of any sulfonamide carries the risk of untoward side effects, including not only rash, fever, and urticaria, but also more serious and in some rare cases potentially fatal complications. Examples are Stevens-Johnson syndrome, toxic epidermal necrolysis, generalized vasculitis, hepatic necrosis, granulocytopenia, aplastic anemia, nephrosis, and hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency.

The second caution concerns the use of TMP-SMX, as distinct from other sulfonamides, for AOM prophylaxis in the United States. Both the current (45th) edition of *Physicians' Desk Reference* and the package inserts accompanying available preparations of TMP-SMX state that this drug combination "is not indicated for prophylactic or prolonged administration in otitis media at any age." On the other hand, no such limitation is specified for preparations of sulfisoxazole. Although this statement is directed at one particular sulfonamide and appears to lack supporting evidence, it might serve to make a physician subject to criticism or to legal liability if an untoward side effect were to occur in a child who was prescribed TMP-SMX for AOM prophylaxis.

REMAINING QUESTIONS

A number of unanswered questions concerning AOM prophylaxis remain. Which drug, at what dosage, offers the optimal combination of efficacy, safety, and cost? Is there a generally optimal duration of prophylaxis, or a valid basis for determining an optimal duration in individual children? Finally, how likely is it that the widespread use of AOM prophylaxis would promote the emergence of resistant strains of organisms in children receiving a particular drug? And if that happened, how great would be the risk of spread of these resistant strains to other children? Answers to these questions are clearly needed to further guide clinical decision-making.

CURRENT RECOMMENDATIONS

Despite the uncertainties that remain, it seems reasonable to offer provisional recommendations. For the child with recurrent AOM, antimicrobial prophylaxis currently appears to be the best first-try intervention available, taking into account safety, efficacy, and cost. Reasonable criteria for undertaking prophylaxis would be the occurrence of at least three episodes of AOM during the preceding 6 months, or at least four episodes during the preceding 12 months provided that at least one episode had occurred within the preceding 6 months. Amoxicillin seems the optimal first choice of drug when patients are not known to be hypersensitive to penicillin. This is primarily because of amoxicillin's long and impressive safety record, and secondarily because of its relatively low cost. For the patient who is hypersensitive to penicillin, or in whom AOM breakthroughs have occurred during amoxicillin therapy, sulfisoxazole is the logical next alternative.

The optimal duration of prophylaxis is, at best, a matter of judgment. Certainly it should continue until the beginning of the following summer season, and for children who have had episodes of AOM during the summer months, probably for at least 1 calendar year.

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SINUSITIS IN INFANTS AND CHILDREN

ELLEN R. WALD, MD
PITTSBURGH, PENNSYLVANIA

The major clinical problem in considering a diagnosis of sinusitis is differentiating uncomplicated upper respiratory tract infection from a secondary bacterial infection of the paranasal sinuses that may benefit from antimicrobial therapy. A diagnosis of sinusitis is suggested by presentation with protracted upper respiratory tract symptoms or a cold that is more severe than usual with fever and purulent nasal discharge. Confirmatory tests of sinus disease are transillumination (useful in adolescents if interpretation is confined to the extremes — normal or absent); radiographic findings of opacification, mucous membrane thickening, or an air-fluid level; and sinus aspiration (indicated for severe pain, clinical failures, or complicated disease). When clinical signs and symptoms are accompanied by abnormal radiographic findings, bacteria in high colony count are recovered from the maxillary sinus aspirate in 70% of patients. The common bacterial species recovered from children with acute maxillary sinusitis are *Streptococcus pneumoniae*, *Moraxella (Branhamella) catarrhalis*, and *Hemophilus influenzae*.

KEY WORDS — antibiotics, bacterial infections, sinusitis, upper respiratory tract infections.

INTRODUCTION

For a clinician considering a diagnosis of sinusitis in a child or an adult, the major problem is to distinguish between, on the one hand, viral upper respiratory tract infection (URI) or allergic inflammation and, on the other hand, secondary bacterial infection of the paranasal sinuses. Both URI and allergy may prompt consideration of symptomatic treatment, whereas patients with sinusitis will benefit from specific antimicrobial therapy. Both URI and allergic inflammation are recognized risk factors for acute sinusitis, with URI being the more common.

PATHOPHYSIOLOGY AND PATHOGENESIS

Three key elements are important to the normal physiology of the paranasal sinuses: the patency of the ostia, the function of the ciliary apparatus, and, integral to the latter, the quality of secretions.[1] Retention of secretions in the paranasal sinuses is due to one or more of the following: obstruction of the ostia, reduction in number or impaired function of the cilia, or overproduction or change in viscosity of secretions.

The ostia of the paranasal sinuses are the key to disease in the sinus area. The ostia of the maxillary sinuses are small tubular structures with a radiologic diameter of 2.5 mm (cross-sectional area about 5 mm) and a length of 6 mm.[2] The diameter of the ostium of each of the individual ethmoid air cells that drain independently into the middle meatus is even smaller, measuring 1 to 2 mm; the anterior are smaller than the posterior.[3] The narrow caliber of these individual ostia sets the stage for obstruction to occur easily and often.

The factors predisposing to ostial obstruction can be divided into those that cause mucosal swelling and those due to mechanical obstruction.[3] The various factors that may cause mucosal swelling, consequent either to systemic illness or to local insults, are shown in Table 1. In addition, those conditions that predispose to mechanical obstruction of the sinus ostia are listed. Although many conditions may lead to ostial closure, viral URI and allergic inflammation are by far the most frequent and most important causes.

CLINICAL PRESENTATION

Commonly recognized symptoms of sinusitis in adults and adolescents are facial pain, headache, and fever. However, children with acute sinusitis frequently have complaints that are less specific. During the course of apparent viral URI, there are two common clinical developments that should alert the clinician to the possibility of bacterial infection of the paranasal sinuses.

The first, most common, clinical situation in which sinusitis should be suspected is persistence of the signs and symptoms of a cold. Nasal discharge and daytime cough that continue beyond 10 days and do not improve are the principal complaints. Most uncomplicated URIs last 5 to 7 days; although

TABLE 1. FACTORS PREDISPOSING TO SINUS OSTIAL OBSTRUCTION

Mucosal Swelling	*Mechanical Obstruction*
Systemic disorder	Choanal atresia
Viral upper respiratory tract infection	Deviated septum
Allergic inflammation	Nasal polyps
Cystic fibrosis	Foreign body
Immune disorders	Tumor
Immotile cilia	
Local insult	
Facial trauma	
Swimming or diving	
Rhinitis medicamentosa	

From the Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.
REPRINTS — Ellen R. Wald, MD, Dept of Pediatrics, University of Pittsburgh School of Medicine, 3705 Fifth Ave, Pittsburgh, PA 15213.

patients may not be asymptomatic by the 10th day they are usually improved. The persistence of respiratory symptoms beyond the 10-day mark without appreciable improvement suggests that a complication has developed.

The nasal discharge may be of any quality (thin or thick; clear, mucoid, or purulent), and the cough (which may be dry or wet) is usually present in the daytime, although it is often noted to be worse at night. Cough occurring only at night is a common residual symptom of a URI. As the only residual symptom, it is usually nonspecific and does not suggest a sinus infection. On the other hand, the persistence of daytime cough is frequently the symptom that brings a child to medical attention. The child may not appear ill, and if fever is present it usually is low-grade. Fetid breath is often reported by parents of preschoolers. Facial pain is absent, but intermittent, painless morning periorbital swelling may have been noted by the parent. In this case, it is the persistence of clinical symptoms and not their severity that calls for attention.

The second, less common, presentation is a cold that seems more severe than usual: the fever is high (greater than 39.0°C), the nasal discharge is purulent and copious, and there is associated periorbital swelling and facial pain. The periorbital swelling may involve the upper or lower lid; it is gradual in onset (evolving over hours to days) and most obvious in the early morning after awakening. The swelling may decrease and actually disappear during the day, only to reappear the following day. A less common complaint is headache (ie, a feeling of fullness or a dull ache either behind or above the eyes), most often reported in children older than 5 years of age. Occasionally, there may be dental pain, either from infection originating in the teeth or referred from the sinus infection.

DIAGNOSIS

Physical Examination. On physical examination, the patient with acute sinusitis may have mucopurulent discharge in the nose or nasopharynx. The nasal mucosa is erythematous; the throat may show moderate injection. The cervical lymph nodes are usually not significantly enlarged or tender. None of these characteristics differentiates rhinitis from sinusitis. Occasionally there will be either tenderness as the examiner palpates over or percusses the paranasal sinuses, appreciable periorbital edema (soft, nontender swelling of the upper and lower eyelid with discoloration of the overlying skin), or both. Malodorous breath (in the absence of pharyngitis, poor dental hygiene, or a nasal foreign body) may suggest bacterial sinusitis.

Transillumination may be helpful in diagnosing inflammation of the maxillary or frontal sinuses. The patient and examiner must be in a darkened room. To transilluminate the maxillary sinus, the light source, shielded from the observer, is placed over the midpoint of the inferior orbital rim. The transmission of light through the hard palate is then assessed with the patient's mouth open. Light passing through the alveolar ridges should be excluded in judging light transmission. Transillumination of the frontal sinus is accomplished by placing a high-intensity light source beneath the medial border of the supraorbital ridge and evaluating the symmetry of the blush bilaterally.

Transillumination is useful in adolescents and adults if light transmission is either normal or absent. Reduced transmission and dull transillumination correlate poorly with clinical disease. The increased thickness of both the soft tissue and bony vault in children less than 10 years of age limits the clinical usefulness of transillumination in the younger age group.[4]

In general, for most children less than 10 years old the physical examination is not very helpful in making a specific diagnosis of acute sinusitis. However, if the mucopurulent material can be removed from the nose and the nasal mucosa is treated with topical vasoconstrictors, pus may be seen coming from the middle meatus. The latter observation and periorbital swelling or facial tenderness (when present) are probably the most specific findings in acute sinusitis.

Radiography. Radiography has traditionally been used to determine the presence or absence of sinus disease. Standard radiographic projections include an anteroposterior, a lateral, and an occipitomental view. The anteroposterior view is optimal for evaluation of the ethmoid sinuses, and the lateral view is best for the frontal and sphenoid sinuses. The occipitomental view, taken after tilting the chin upward 45° from the horizontal, allows evaluation of the maxillary sinuses.

Although much has been written about the frequency of abnormal sinus radiographs in "normal" children, these studies have been flawed either by inattention to the presence of symptoms and signs of respiratory inflammation or by failure to classify abnormal radiographic findings as major (significant) or minor (insignificant).[5,6] One report[7] shows that abnormal maxillary sinus radiographs are infrequent in children beyond their first birthday who are without recent symptoms and signs of respiratory tract inflammation.

The radiographic findings most diagnostic of bacterial sinusitis are the presence of an air-fluid level in, or complete opacification of, the sinus cavities. However, an air-fluid level is an uncommon radiographic finding in children less than 5 years of age with acute sinusitis. In the absence of an air-fluid level or complete opacification of the sinuses, measuring the degree of mucosal swelling may be useful. If the width of the sinus mucous membrane is 5 mm or greater in adults or 4 mm or greater in children, the sinus is likely to contain pus or yield a positive bacterial culture.[8,9] When clinical signs and symptoms suggesting acute sinusitis are accompanied by abnormal maxillary sinus radiographic findings, bacteria will be present in a sinus aspirate 70% of the time.[9] A normal radiograph suggests, but does not prove, that a sinus is free of disease.

Sinus Aspiration. The diagnosis of acute bacterial sinusitis is probably best proved by a biopsy of the sinus mucosa that demonstrates acute inflammation and invasion by bacteria. In practice, confirmation of the diagnosis is more often accomplished by culturing an aspirate of sinus secretions. Nonetheless, when simultaneously obtained mucosal biopsies and sinus aspirates are submitted for bacterial cultures, biopsies more often yield positive results.

Although by no means a routine procedure, aspiration of the maxillary sinus (the most accessible of the sinuses) can be accomplished easily in an outpatient setting with minimal discomfort to the patient. Puncture is best performed by the transnasal route with the needle directed beneath the inferior turbinate through the lateral nasal wall. This route for aspiration is preferred to avoid injury to the natural ostium and permanent dentition. If the patient is unusually apprehensive or too young to cooperate, a short-acting narcotic agent can be used for sedation.

Careful sterilization of the puncture site is essential to prevent contamination by nasal flora. Four percent cocaine solution applied intranasally will achieve mucosal anesthesia and antisepsis. Lidocaine hydrochloride (Xylocaine) should be injected into the submucosa at the site of the actual puncture. Secretions obtained by aspiration should be submitted for Gram stain and quantitative aerobic and anaerobic cultures. Bacterial isolates should be tested for their sensitivity to various antibiotics. A high bacterial colony count ensures that the culture results reflect actual sinus infection rather than contamination; counts of greater than 10^4 colony-forming units per milliliter give a high degree of assurance of in situ infection. Alternatively, examination of a Gram stain preparation of sinus secretions may be helpful, as bacteria that are present in low colony count (likely to be contaminants) will usually not be seen on smear.

Indications for sinus aspiration in patients with suspected sinusitis include clinical unresponsiveness to conventional therapy, sinus disease in an immunosuppressed patient, severe symptoms such as headache or facial pain, and life-threatening complications such as intraorbital or intracranial suppuration at the time of clinical presentation.

MICROBIOLOGY

Knowledge of the bacteriology of secretions obtained directly from the maxillary sinus by needle aspiration (with careful avoidance of contamination from mucosal surfaces) provides information essential to planning antimicrobial therapy.

TABLE 2. BACTERIOLOGY OF ACUTE SINUSITIS

Organism	*Prevalence (%)*
Streptococcus pneumoniae	25-30
Moraxella (Branhamella) catarrhalis	15-20
Hemophilus influenzae	15-20
Streptococcus pyogenes	2-5
Anaerobes	2-5
Sterile	20-35

Whether there is a normal flora of the paranasal sinuses is an area of controversy. It is the opinion of some, and there are scant data to support the notion, that the paranasal sinuses are normally sterile. On the other hand, in a study of adults undergoing correction of nasal septal deviation,[10] anaerobic and aerobic bacteria were recovered from the sinus aspirates of all individuals. The question here is whether such patients constitute a normal population. Septal deviation is a known risk factor for sinusitis and radiographs were not obtained prior to sinus puncture in these individuals. It will be difficult to resolve this controversy, because the violation of normal sinus cavities can rarely be justified.

A study of 50 children with acute maxillary sinusitis[11] has shown the bacteriology of sinus secretions to be similar to that found in adults.[12] The predominant organisms include *Streptococcus pneumoniae*, *Moraxella (Branhamella) catarrhalis*, and nontypeable *Hemophilus influenzae*. Both *H influenzae* and *M catarrhalis* may produce β-lactamase and, consequently, may be ampicillin-resistant. Interestingly, only a single anaerobic isolate, a *Peptostreptococcus* species, was recovered from sinus secretions during this study. *Staphylococcus aureus* was not isolated from a maxillary sinus aspirate. Several viruses, including adenovirus and parainfluenzae, were also recovered.[11] Summary figures for the prevalence of various bacterial species in children with acute sinusitis are shown in Table 2.

It would be desirable to culture the nose, throat, or nasopharynx in patients with acute sinusitis if the predominant flora isolated from these surface cultures were predictive of the bacterial species recovered from the sinus secretions. Unfortunately, the results of surface cultures have no predictive value; accordingly, nose, throat, and nasopharyngeal cultures cannot be recommended as guides to the bacteriology and therapy of acute or chronic sinusitis.[9]

TREATMENT

Therapy for acute maxillary sinusitis in the preantibiotic era consisted of sinus aspiration and irrigation. The current availability of numerous antimicrobial agents to which the bacteria recovered from sinus secretions are susceptible prompts con-

TABLE 3. ANTIMICROBIAL AGENTS FOR ACUTE SINUSITIS

Drug	*Dosage*
Amoxicillin	40 mg/kg per day in 3 divided doses
Erythromycin ethylsuccinate and sulfisoxazole acetyl	50 mg/kg and 150 mg/kg per day in 4 divided doses
Sulfamethoxazole and trimethoprim	40 mg/kg and 8 mg/kg per day in 2 divided doses
Cefaclor	40 mg/kg per day in 3 divided doses
Amoxicillin and clavulanate potassium	40 mg/kg and 10 mg/kg per day in 3 divided doses
Cefixime	8 mg/kg once daily

sideration of antimicrobials as standard treatment of acute sinusitis. The objectives of antimicrobial therapy are achievement of a rapid clinical cure, sterilization of the sinus secretion, prevention of suppurative orbital and intracranial complications, and prevention of chronic sinus disease.

Antimicrobial Agents. Medical therapy with an antimicrobial agent is recommended in children with acute maxillary sinusitis. The relative frequency of use of the various bacterial agents suggests that amoxicillin is the appropriate agent for most uncomplicated cases of acute sinusitis (Table 3). Amoxicillin is relatively safe, effective, and reasonably priced. Safety is an especially important consideration when treating an infection with a 40% rate of spontaneous recovery.[4] The prevalence of β-lactamase–positive, ampicillin-resistant *H influenzae* and *M catarrhalis* may vary geographically. In cases of prevalent ampicillin-resistant organisms, patient allergy to penicillin, accompanying mild periorbital swelling, or apparent antibiotic failure, several alternative regimens are available. The combination agent trimethoprim-sulfamethoxazole (Bactrim, Septra) has been shown to be efficacious in acute maxillary sinusitis in adults. However, this combination agent may be ineffective in patients with group A streptococcal infections. A combination of amoxicillin and clavulanate potassium (Augmentin) is a therapeutic agent for use in patients with β-lactamase–producing bacterial species in maxillary sinus secretions. Clavulanate potassium irreversibly binds the β-lactamase, if present, and thereby restores amoxicillin to its original spectrum of activity.

Cefaclor (Ceclor) and the combination erythromycin ethylsuccinate–sulfisoxazole acetyl (Pediazole) are also suitable agents. Cefixime (Suprax) is a third-generation cephalosporin with excellent activity against β-lactamase–producing *H influenzae* and *M catarrhalis*; it has no activity against *S aureus* and marginal activity against *S pneumoniae*. It should be reserved for use in patients whose infections fail to respond to amoxicillin.

Patients with acute sinusitis may require hospitalization because of systemic toxicity or inability to take oral antimicrobials. These patients may be treated intravenously with cefuroxime axetil (Ceftin), 100 to 200 mg/kg per day in three divided doses.

Clinical improvement is prompt in nearly all children treated with an appropriate antimicrobial agent. Patients febrile at the initial encounter will become afebrile, and there is a remarkable reduction of nasal discharge and cough within 48 hours. If the patient does not improve or worsens in 48 hours, clinical reevaluation is appropriate. If the diagnosis is unchanged, sinus aspiration may be considered to obtain precise bacteriologic information. Alternatively, an antimicrobial agent effective against β-lactamase–producing bacterial species should be prescribed.

The antimicrobial regimens recommended for treatment of acute sinusitis are similar in type and duration to those used for acute otitis media. The usual duration of antimicrobial therapy is 10 to 14 days. This recommendation is based on an experience in adults that demonstrated that 20% of sinus aspirates obtained after 7 days of antimicrobial treatment were still culture-positive.[8] When the patient is improved but not completely recovered by 10 or 14 days, continuation of treatment for another week is reasonable.

Decongestants and Antihistamines. The effectiveness of antihistamines, decongestants, or combinations thereof applied topically (by inhalation) or administered by mouth in acute or chronic sinus infection has not been adequately studied. Limited investigation of specific agents in clinical rhinitis has shown that some produce a decrease in nasal resistance. However, a study of patients with sinorhinitis[13] found that oral phenylpropanolamine hydrochloride did not significantly increase the size of the maxillary ostium.

Topical decongestants such as phenylephrine hydrochloride or oxymetazoline hydrochloride shrink the nasal mucous membrane, improve ostial drainage, and provide symptomatic improvement; however, they may cause ciliostasis. Ciliary motion is an important local defense mechanism; the entire mucous covering of the maxillary antrum is normally cleared every 10 minutes. By inhibiting ciliary motion, topical decongestants may delay clearance of infected material. In addition, by decreasing blood flow to the mucosa, topical decongestants may further lower oxygen tension and impair diffusion of antimicrobial agents into the sinuses. The net effect of the various topical preparations on clinical recovery from sinusitis or the incidence of complications is unknown.

Irrigation and Drainage. Irrigation and drainage of the infected sinus may result in dramatic relief from pain for patients with acute sinusitis. In addition, with relief of pressure in the sinus, oxygenation and blood flow improve, thus restoring compromised defense mechanisms. Local immunoglobulin and complement levels increase and proteolytic enzymes decrease in sinus secretions after irrigation procedures. Drainage procedures are usually reserved for those whose condition fails to respond to medical therapy with antimicrobial agents or who have a suppurative intraorbital or intracranial complication. If an episode of acute sinusitis cannot be effectively treated by medical therapy alone or medical therapy and simple sinus puncture, more radical surgery may be necessary.

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SURGICAL MANAGEMENT OF SINUS DISEASE IN CHILDREN

SCOTT C. MANNING, MD
DALLAS, TEXAS

In the past few years, interest in pediatric sinus surgery has increased in response to the introduction of new endoscopic techniques and to mounting societal pressure to resolve the problem of persistent rhinosinusitis in the day-care setting. As yet, there are no prospective controlled studies demonstrating efficacy of sinus surgery in children with uncomplicated acute or recurrent acute sinusitis, and medical management overwhelmingly remains the treatment of choice for these patients. Sinus surgery may be indicated, however, for three groups of pediatric patients: those with true chronic disease, those with serious underlying disease states aggravated by recurrent sinusitis, and those with suppurative complications of sinusitis.

KEY WORDS — pediatric sinus surgery, rhinosinusitis, sinusitis.

INTRODUCTION

Otolaryngologists are often presented, by parents and pediatricians, with the problem of a child with chronic rhinorrhea and/or cough. Increasingly, the possibility of surgery as a treatment for presumed chronic sinusitis arises. This heightened interest in pediatric sinus surgery derives from two relatively recent phenomena: 1) children in day-care who have greater exposure to routine viral illness and parents who have less time for routine care of such illnesses, and 2) the development of newer endoscopic techniques for sinus surgery with the expectation, not necessarily valid, of achieving better results with less morbidity. Which treatment is best for a child with sinusitis is not always clear; there is little evidence, however, that chronic rhinorrhea results in long-term morbidity for most children, or that pediatric sinus surgery necessarily results in long-term improvement. The surgeon must deliberate carefully in deciding which few pediatric patients are likely to have a high enough benefit-to-risk ratio to justify surgical intervention.

DIAGNOSIS

The first hurdle that must be overcome in selecting potential surgical candidates is diagnosis. Children are relatively poor historians, and the signs and symptoms of pediatric sinusitis (cough, rhinorrhea, lethargy, hoarseness, etc) are notoriously nonspecific. Children have relatively shallow sinuses with relatively wide ostia, and are therefore less likely than adults to present with more specific signs and symptoms of pus under pressure. For the same reason, there is less likelihood that true chronic sinus obstruction will develop, and thus that surgical procedures to increase drainage and ventilation will be of benefit. The point at which routine mucosal rhinosinusitis becomes refractory sinusitis that might benefit from mechanical drainage and ventilation is extremely difficult to determine in children.

Radiographic findings are also extremely nonspecific in the pediatric population. Several studies have demonstrated that mucosal thickening, by far the most common finding, is poorly associated with clinical sinusitis in children younger than age 6.[1-3] In patients of any age, an air-fluid level strongly correlates with clinical disease, while clear sinuses correlate with absence of clinical disease.[4]

Computed tomography (CT) is the diagnostic procedure of choice when surgery is contemplated, or when suppurative complications of sinusitis are suspected. Coronal views are preferred in order to demonstrate the anatomy from the surgeon's perspective; general anesthesia may be necessary to obtain such views in young children. Mucosal thickening may indicate not clinical sinusitis but an ongoing or resolving upper respiratory tract infection (URI); it is an extremely common finding among pediatric patients without sinus symptoms who are undergoing CT for other reasons. As Wald et al[5] reported in 1981, radiographic findings must be correlated with clinical signs and symptoms of sinusitis to have useful sensitivity and specificity, and therefore do not in themselves constitute an indication for surgery.

MEDICAL MANAGEMENT

In most reported series of pediatric sinus surgery, the indication is given as failure of medical management.[6,7] Unfortunately, there is no consensus regarding the optimum length of treatment for acute sinusitis in children, although relapses are common with the usual 7- to 10-day course.

In recurrent or refractory sinusitis, 3- to 4-week courses of broad-spectrum antibiotics effective against β-lactamase–producing *Hemophilus influenzae* are indicated prior to consideration of surgery. If signs and symptoms resolve with antibiotic therapy, a once-a-day prophylactic antibiotic regimen for another 6 weeks or so may be considered.

From the Department of Otolaryngology, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas.
REPRINTS — Scott C. Manning, MD, Dept of Otolaryngology, 5323 Harry Hines Blvd, Dallas, TX 75235-9035.

In addition, twice-daily nasal saline irrigations are useful as an efficient means of humidifying the nasal mucosa. This has the added advantage of removing secretions and crusts, and improving sinus drainage via mild vasoconstriction.

Antihistamine decongestant preparations are useful for acute congestion. With long-term use, however, they may lead to problems that result from mucosal drying and impairment of mucociliary defense mechanisms. There are no prospective studies demonstrating efficacy of these preparations for recurrent or chronic sinusitis. Finally, since inhalant allergy is, after viral illness, the second most common predisposing factor in pediatric sinusitis, allergy evaluation is indicated for any patient for whom surgery is being considered because of recurrent or refractory disease. Nasal steroid preparations such as beclomethasone dipropionate (Beconase, Vancenase) are approved for children age 6 or older, and cromolyn sodium (Intal, Nasalcrom) may be used at younger ages.

SURGICAL MANAGEMENT

In adults, sinus surgery is indicated principally for two groups of patients: those with true chronic disease, ie, irreversible disease despite maximal medical care; and in cases of suppurative complications, ie, when disease spreads beyond the confines of the sinuses to involve adjacent structures. In the pediatric population, a third category of patients may benefit from sinus surgery: those in whom sinusitis aggravates serious underlying disease states such as asthma or cystic fibrosis. Surgery can remove diseased tissue and improve sinus drainage and ventilation, but it cannot address underlying predisposing factors such as allergy. It should therefore be considered primarily as an adjunct to medical therapy.

Pediatric sinus procedures can be divided into two groups: indirect measures to improve nasal and sinus function, and direct surgery on the sinuses themselves. Indirect measures include limited nasal septoplasty, used when an obvious obstruction appears linked to persistent or recurrent ipsilateral disease; removal of foreign bodies; and polyp excisions. Tonsillectomy and adenoidectomy have long been anecdotally associated with improvement in nasal symptoms in young children, but prospective controlled trials are lacking. Takahashi et al[8] demonstrated statistically significant improvement in sinusitis in young children 6 months following adenoidectomy, compared with no-surgery controls, using plain radiographs as the outcome measurement. The effect appeared to be unrelated to the size of the adenoidal tissue; removal of the tissue itself was therefore felt to be secondary to removal of the adenoid as a source of chronic inflammation.

Sinus Lavage. The least invasive and probably most common direct sinus procedure performed directly on the sinuses in the pediatric age group is lavage. The recovery rate of abnormal sinus fluid with lavage is low in this population, and few studies have addressed overall efficacy of the procedure.[3] Otten and Grote[9] divided 141 children with no comorbid disease and with chronic maxillary sinusitis documented by physician examination and radiography into four groups: placebo, amoxicillin plus decongestant, sinus lavage, and lavage plus antibiotics. There was no difference among the groups in clinical or radiographic evidence of sinusitis at 6 months. The investigators concluded that uncomplicated maxillary sinusitis in children is usually a self-limiting process. Sinus lavage requires general anesthesia in young children and is not without the potential for serious complications. Absolute indications include rapid culturing and appropriate antibiotic selection for patients with serious immunodeficiencies.

Antrostomy. Nasal antral window procedures provide a more lasting means of maxillary sinus drainage and ventilation, but again, studies demonstrating efficacy are lacking. Inferior meatus antrostomies tend to close quickly in children, perhaps because the natural mucociliary flow is via the middle meatus. Middle meatus antrostomy is technically challenging in young children because of the small distance between the lateral nasal wall and the orbit. Also, antrostomy procedures do not address the anterior ethmoids, which are probably the most commonly diseased sinuses in both children and adults. In a retrospective review, Muntz and Lusk[10] recently reported only a 27% "success" rate with nasal antral window procedures.

Caldwell-Luc Procedures. Caldwell-Luc procedures are applied with decreasing frequency in the pediatric population. Unerupted teeth are at significant risk with this approach, and stripping of all maxillary sinus mucosa in a child can result in permanent sinus hypoplasia. There are probably a few instances in which maxillary sinus mucosa is truly irreversibly diseased in children, and therefore deserving of total removal. Suspected maxillary sinus neoplasm is one instance in which a Caldwell-Luc procedure may be indicated.

Endoscopic Surgery. With nasal respiration, the middle meatus and anterior ethmoid are the regions of maximum particle deposit. It is likely that this area bears the brunt of mucosal disorder with allergic, viral, and bacterial disease. That the middle meatus is the area of confluence of mucociliary drainage from all the sinuses results in the disruption of mucociliary clearance, as demonstrated by Messerklinger.[11] The fundamental concepts underlying endoscopic sinus surgery are that patent ostia are the keys to sinus health via drainage and ventilation, and that limited mucosal disease in the area of the anterior ethmoids and middle meatus can involve all the sinuses by blocking drainage and ventilation. Therefore, limited surgical opening of this area (usually an endoscopic anterior ethmoidectomy and middle meatus antrostomy) may allow diseased mucosa in all sinuses to return to normal by restoring normal sinus physiology.[12]

Only in the last few years have endoscopic sinus surgeons in the United States ventured into the more restricted confines of the pediatric nose. This represents a natural broadening of the indications for sinus endoscopy, as surgeons become more familiar and experienced with the necessary techniques. The few reported pediatric case series are optimistic, but follow-up has been short. There are no prospective controlled studies to guide the surgeon regarding indications. Gross et al[6] retrospectively studied 57 children with "chronic" sinusitis who underwent endoscopic sinus surgery and reported generally good results, as determined by parental questionnaire. Lusk and Muntz[7] recently reported on 31 patients with a 71% 1-year success rate, also assessed by parental questionnaire.

INDICATIONS FOR SURGERY

There is no generally accepted definition of chronic or recurrent sinusitis as a surgical indication in children. The average child has six to eight viral URIs per year, and sinusitis is generally suspected when signs and symptoms persist beyond 10 days. Some authors have suggested the diagnosis of recurrent sinusitis when a child has a history of three episodes in 6 months or four in 1 year. The otolaryngologist, however, often sees a patient only after he or she has had multiple treatments with antibiotics and decongestants, and distinguishing separate episodes can be difficult.

True recurrent or chronic sinusitis implies anatomic obstruction of sinus ostia, a problem with a local mucociliary defense mechanism such as cystic fibrosis, or a systemic immune problem. Sinus surgery obviously can directly address only an anatomic cause, which is rarely the primary problem in children. Surgery also has the potential for greater risk in children than in adults because of a more restricted surgical field with greater proximity of adjacent structures such as orbit and brain. This fact, combined with the lack of any prospective studies demonstrating efficacy of surgery for routine "chronic" sinusitis, should severely limit indications for sinus surgery in the majority of otherwise healthy children with sinus and nasal symptoms.

Suppurative Complications. The need for sinus surgery in children is not controversial when there is suppurative involvement of adjacent anatomic structures. Sphenoid and frontal sinusitis is, fortunately, unusual in children, but such cases require extra attention because of the greater propensity for infection to lead to meningitis, subdural or epidural empyema, or brain abscess. Symptomatic children with radiographic evidence of sphenoid disease refractory to antibiotics require sphenoid drainage. In any patient with frontal sinusitis who has forehead tenderness or edema or with possible central nervous system symptoms such as lethargy, surgical drainage will be necessary if improvement does not occur within a short time with intravenous administration of antibiotics. In the case of suppurative orbital disease, drainage of adjacent infected sinuses is indicated as an adjunct to primary abscess drainage.

Cystic Fibrosis, Asthma, and Immunodeficiencies. The three most common significant comorbid diseases associated with pediatric sinusitis are cystic fibrosis, asthma, and immunodeficiency. Recurrent flare-ups of sinusitis in patients with these conditions often have a significant negative impact on overall health; the threshold for recommending adjunctive sinus surgery is therefore lower.

The reported incidence of nasal polyposis and sinusitis in cystic fibrosis patients varies from 5% to 40%. The diagnosis should be considered in any child with unusually severe or recurrent sinusitis, even in the absence of nasal polyps. Cystic fibrosis patients with significant sinusitis and/or polyposis should first be managed medically, but they often eventually require surgery for best control of symptoms. Parents often report deterioration in pulmonary status in conjunction with worsening nasal problems. This deterioration may be secondary to direct seeding of the lungs by infected sinus secretions or to the impact of loss of normal nasal function on already compromised lungs. In the past, limited polypectomy was considered the procedure of choice in such cases, but recurrence rates were extremely high. There are indications that more extensive surgery, including the involved ethmoid sinuses, provides much better long-term results.[13,14]

Several authors have noted that asthma may be more severe and more difficult to control in the presence of chronic and recurrent sinusitis. Rachelefsky et al[15] noted a strong correlation between resolution of sinus disease and ability to discontinue bronchodilator therapy in a group of 48 children with asthma and sinusitis. Friedman et al,[16] in a study of 7 children with difficult-to-control asthma and sinusitis, demonstrated improvement in pulmonary function tests with resolution of sinusitis in 5 subjects. When evaluating patients with cystic fibrosis and asthma, the surgeon must, of course, keep in mind that chronic pulmonary disease increases the likelihood of perioperative morbidity.

Clinicians must consider the possibility of local or systemic problems with immune defenses in any child with chronic or recurrent sinusitis. The most common manifestation of primary immunodeficiency may be the propensity of young children to suffer from increased numbers of URIs because of normal delays in immunoglobulin (Ig) G subclass maturation. Immunoglobulin G2 and IgG4, in particular, play an important role in immune defense against polysaccharide-encapsulated bacteria such as *Streptococcus pneumoniae* and *H influenzae*,[17] and do not reach adult levels until late childhood. Thus, very young and otherwise healthy children with chronic rhinosinusitis are best managed medically, to allow immune maturation to occur.

Immune system evaluation is indicated in children with a history of other unusual or unusually severe recurrent infections such as pneumonia, or with recurrent rhinosinusitis showing no improvement after age 3. When levels of IgG subclasses are low or borderline-low for a child's age, polysaccharide vaccine antibody response is indicated to determine clinical relevancy.[18] Children with sinusitis secondary to immune deficiencies, such as those of the IgA or IgG subclasses, are best managed medically. However, sinus surgery may be a useful adjunct to remove loculations of persistent disease in selected cases.

The most common acquired immunodeficiencies associated with pediatric sinusitis include those in organ transplant patients, cancer patients, and patients with acquired immunodeficiency syndrome. Renal transplant patients on steroid therapy in the first year after surgery are at greatest risk for invasive fungal sinusitis, with *Aspergillus* species the most common pathogen. Pediatric patients receiving chemotherapy for lymphoreticular malignancies are also at high risk for fungal sinusitis. With invasive disease, appropriate surgery consists of wide excision of involved tissues; unfortunately, the sinus condition is rarely resolved if the underlying immunodeficiency cannot be reversed. Sinusitis in patients with acquired immunodeficiency syndrome is usually treated medically; surgery may be indicated, however, when suppurative complications exist or when aggressive medical treatment fails.

SUMMARY

Surprisingly little research has focused on the natural history of routine recurrent sinusitis in children. It appears, however, that the majority of patients eventually outgrow the condition without significant morbidity along the way. Sinus surgery is indicated when the disease involves adjacent structures such as the orbit, when disease significantly aggravates underlying health-threatening conditions such as asthma, and when definite areas of anatomic obstruction can be causally linked to disease. True chronic disease is, by definition, less likely in younger children, and the risks of surgery are greater in this age group. Chronic rhinorrhea is, in itself, not a valid indication for pediatric sinus surgery.

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MEDICAL AND SURGICAL MANAGEMENT OF SINUSITIS IN ADULTS

WILLIAM J. RICHTSMEIER, MD, PHD
BALTIMORE, MARYLAND

Sinusitis may be caused by bacteria, viruses, or trauma and may appear in immunosuppressive settings. Acute sinusitis is most commonly diagnosed on the basis of pain and discharge; endoscopic or fiberoptic examination may be helpful in less obvious cases. Radiography can identify maxillary, frontal, and sphenoid sinusitis; transillumination can be used if radiography is undesirable. Culture and Gram stains may help determine the appropriate antibiotic therapy. Surgery may be necessary if the frontal or sphenoid sinus is involved, or if ethmoiditis is progressing to orbital cellulitis. In chronic sinusitis, endoscopic examination and computed tomographic scanning are useful for diagnosis. Chronic sinusitis may be associated with airway disease, aspirin allergy, and such diseases as cystic fibrosis. Antibiotic therapy that acts against anaerobes and β-lactamase-producing organisms should be chosen. Surgical treatment includes intranasal and external ethmoidectomy, antrostomy, and, on occasion, obliteration of the involved cavity.

KEY WORDS — acute sinusitis, chronic sinusitis, endoscopy, ethmoidectomy.

INTRODUCTION

Treatment of the symptoms of sinusitis — difficult to distinguish from those of the common cold and allergy, and thus often misinterpreted by the public — is responsible for a billion-dollar-per-year industry in pharmaceuticals and an enormous amount of time lost from work. While acute sinusitis is relatively uncommon, chronic sinusitis is being seen with increasing frequency, as clinicians become better able to diagnose chronic ethmoiditis with newer diagnostic and radiologic imaging procedures. This paper summarizes current thinking about causes, diagnosis, and management of both acute and chronic sinusitis.

ACUTE SINUSITIS

ETIOLOGY

Acute sinusitis may result from exposure to virulent organisms that an individual has not previously encountered, such as a new subtype of pneumococcus. Trauma, such as a direct penetrating injury or maxillary and ethmoid fractures, can obstruct the sinus and lead to an acute problem, particularly when blood within the sinus provides fertile ground for bacterial growth. Iatrogenic causes are another form of trauma; introduction of blood into the sinus through a transmaxillary approach to the pterygoid space or placement of nasogastric feeding tubes may obstruct sinus ostia, leading to acute sinusitis. Barosinusitis is a recognized acute cause of pain, but probably has an underlying chronic obstructive component.

Occasionally, acute sinusitis is seen in a setting that is considered immunosuppressive; the edematous nasal mucosa that frequently occurs during pregnancy, for example, appears to compromise a rapid response to sinus infection. Even the changes in nasal mucociliary transport associated with an allergic response can be thought of as immunosuppressive, since transport of the mucous blanket is an important part of first-line defense against infecting organisms.

More commonly, viral infections that are clearly immunosuppressive, such as human immunodeficiency virus (HIV) infection, can give rise to acute sinusitis. Other, not so well-known viruses such as Epstein-Barr virus can also induce a prolonged immunosuppressive state. In this case, the body's normal (and appropriate) response is to try to suppress B cell proliferation of the Epstein-Barr virus; unfortunately, in the process, normal responses controlled by the T cell system are also suppressed.

Some individuals have anatomic conditions that predispose them to infections with minimal outside insult. Those with long infundibular tracts or stenotic maxillary sinus ostia, for example, may be more likely to suffer from acute sinusitis.

DIAGNOSIS

The diagnosis of acute sinusitis is often readily made on the basis of a history of acute pain, purulent discharge, and, in many cases, fever. In severe cases, the patient will appear seriously ill. This is particularly true when involvement extends beyond the sinuses proper, as when orbital cellulitis or acute ethmoiditis accompanies sinusitis.

Diagnosis in less obvious cases is facilitated by endoscopic examination; small amounts of purulent material can often be seen emerging from the infundibulum, sphenoid ostia, or occasionally from an anterior direct frontal sinus. Subtle changes in color, thickness, and vascularity of the mucosa of the middle meatus can be readily appreciated, and purulent discharges can be identified and discretely sampled. Hoffman endoscopes, in particular, produce a superior telescopic image.

From the Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins Medical Institutions, Baltimore, Maryland.

REPRINTS — William J. Richtsmeier, MD, PhD, Dept of Otolaryngology-Head and Neck Surgery, Johns Hopkins Hospital, 600 N Wolfe St, Carnegie 469, Baltimore, MD 21205.

Flexible fiberoptic scopes are an improvement over simple anterior rhinoscopy and are of great value to the clinician who does not have an endoscope available. Fiberoptic scopes can be readily introduced into the middle meatus. By sliding the scope along the floor of the nose underneath the inferior turbinate and extending it superiorly into the sphenoethmoidal recess, the examiner can perform diagnostic maneuvers similar to those possible with lens endoscopes. Flexible scopes, however, do not provide the image clarity obtained with endoscopes, and make it virtually impossible to perform discrete diagnostic sampling for cultures.

Routine radiographic studies are often positive in cases of acute maxillary sinusitis, but may not be particularly helpful in isolated ethmoiditis. Acute frontal sinusitis and sphenoid sinusitis are also well visualized by routine radiographic studies, as an air-fluid level or complete opacification is easily recognized. Transillumination as part of a routine examination can be useful when repeated radiographic studies are undesirable (for example, in the treatment of acute sinusitis during pregnancy). In such cases, resolution of the sinusitis can be followed by transillumination if a clear difference between the two sides can be observed, eliminating the need for follow-up radiographs.

Acute sinusitis can be caused by either viral or bacterial infection; in mixed viral-bacterial sinusitis, it is theorized, the viral component causes sinus obstruction that allows the pathogenic bacteria to grow.[1] An acute obstruction to air exchange may be needed to induce the significantly increased numbers of anaerobic organisms seen in maxillary sinusitis.

TREATMENT

Antibiotics. Acute sinusitis is poorly understood by the nonotolaryngologic community, and it is surprising how seldom antibiotics are used in its management, since there are clear indications for antibiotic use to relieve the discomfort that accompanies acute sinusitis. Cultures of recovered organisms and Gram stains can be helpful in determining appropriate initial antibiotic therapy. For example, the appearance of diplococci in a Gram stain would suggest treatment with an agent such as penicillin. On the other hand, the presence of small gram-negative rods might dictate use of a more broad-spectrum antibiotic that would encompass treatment of β-lactamase–producing *Hemophilus*, particularly during a time when resistant *Hemophilus* has been found in the community.

When a patient does not respond to therapy with a limited-spectrum antibiotic, coverage for both β-lactamase–producing *Hemophilus* and more unusual organisms should be considered. Decongestants often help to open the middle meatus and relieve congestion, and may contribute to relief of pain. It should be remembered, however, that topical decongestants may interfere with nasal cilia motility, thereby inhibiting mucociliary transport.

Surgery. Surgical treatment of uncomplicated acute sinusitis is not indicated unless the frontal or sphenoid sinus is involved. Maxillary and ethmoid sinusitis can usually be treated with antibiotics and decongestants. Many patients with acute maxillary sinusitis improve symptomatically with lavage. An approach via the inferior meatus rather than the canine fossa is usually chosen, since pressure on the sinus associated with nose-blowing can move purulent material into the premolar space and contaminate it.

When ethmoiditis is thought to be progressing to orbital cellulitis, a decision for aggressive decompression must be made on the basis of symptoms and concern for the integrity of the eye. At Johns Hopkins Hospital, we are usually surgically aggressive in this situation, as we have never seen visual improvement in patients, even with surgical intervention, once they have progressed to loss of vision associated with orbital cellulitis. Since visual loss can occur rapidly, it is difficult simply to observe such patients for potential complications. Transnasal decompression of the sinus, especially with the use of an endoscope, is being used more often by those skilled in this maneuver. However, adequate decompression must be clearly obtained, and radiographic follow-up is generally required. The more traditional approach of external sinusotomy — particularly in frontal sinusitis — is relatively safe and effective and should be considered when the response to medical therapy is slow. As implied earlier, external sinusotomies are rarely indicated for uncomplicated acute maxillary or ethmoid sinusitis.

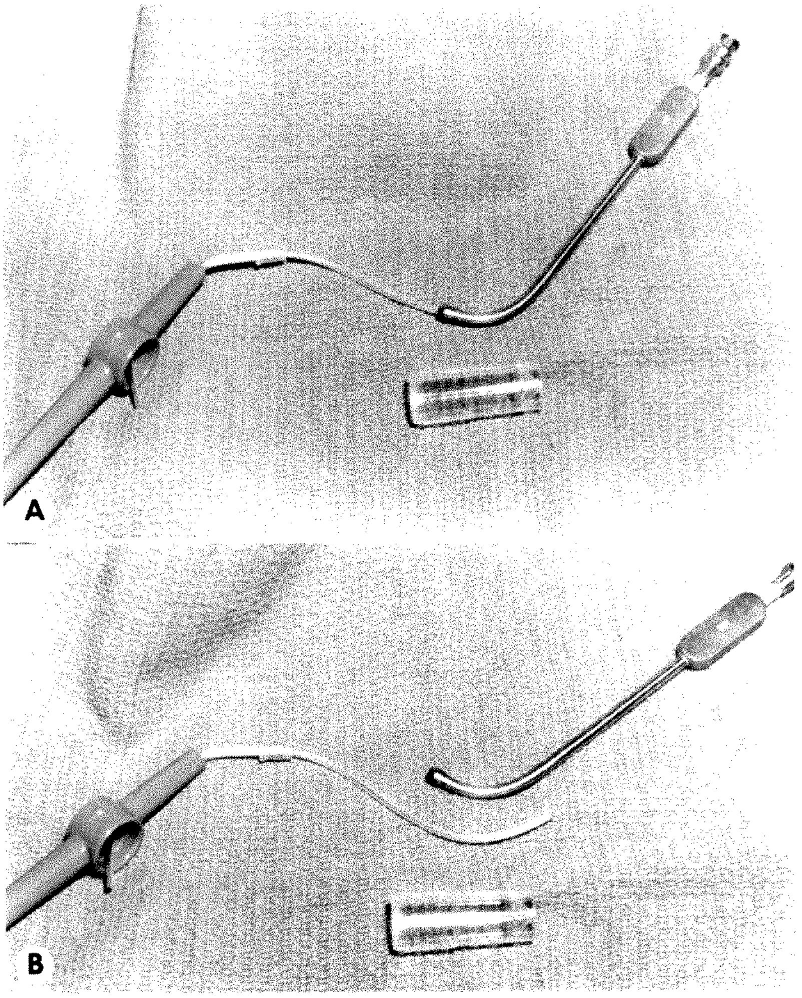
CHRONIC SINUSITIS

Acute sinusitis usually resolves within 3 weeks of onset. Some acute cases may persist longer before clearing up, but after 9 to 10 weeks the disease is unlikely to resolve as an acute process and can be labelled chronic. Because the extent of disease may be greater when this stage is reached, diagnosis and management of chronic sinusitis differs from that of acute sinusitis.

DIAGNOSIS

Research pioneered by Messerklinger,[2] Stammberger,[3,4] and Kennedy and Zinreich[5] in recent years has contributed enormously to our knowledge about the functional anatomy of the ethmoid ostiomeatal complex, and to our understanding of chronic sinusitis. As described by Proctor[6] and discussed by Ritter,[7] pathogenesis of both maxillary and frontal sinusitis shows a central role of the anterior ethmoidal complex as well as of the ethmoid itself.

Computed tomographic scanning of the sinuses, as described by Zinreich et al,[8] has allowed docu-



Technique for bending plastic tubing to cannulate sinus ostium. A) Tubing is inserted into barrel of sterile, large-bore, curved suction cannula used for endoscopic surgery. B) After brief heat exposure (in hot bead sterilizer), plastic "remembers" shape of metal suction cannula. Disposable plastic cannula remains sterile throughout procedure. Choice of curve of metal cannulae and variation of plastic cannula's angle of rotation to thumb vent on disposable aspirator allow fabrication of disposable cannula unique to each patient's anatomy.

mentation and clarification of areas of infection and strongly supports the use of endoscopic examination. Computed tomographic scans also provide a tool with which the physician can explain to the patient the functional anatomy of the area, the relationship of anatomy to sinusitis symptoms, and the risks of surgery. As with acute sinusitis, the endoscopic examination — particularly with the Hoffman scope — is extremely useful.

There are a number of diseases associated with chronic sinusitis. The most common conditions are reactive airway syndromes such as allergic rhinitis, but they can extend to the complex of severe polyposis, aspirin allergy, and reactive airway disease. Other diseases, such as those that inhibit mucociliary transport (ie, cystic fibrosis or primary abnormalities of ciliary motility), may be present. In patients with recurrent acute infection, a screen for selective IgA deficiency or common variable immunodeficiency is indicated.[1] Cultures obtained prior to treatment are extremely important, as many cases of chronic sinusitis are associated with organisms other than those familiar to physicians treating the acute form.

Microbiology of the maxillary sinus in chronic disease shows a significant increase in the number of anaerobic organisms compared to that seen in the acute form.[9,10] While aerobes similar to those found in acute sinusitis are observed, there is a significant increase in *Staphylococcus aureus* infections, which are not usually seen in acute sinusitis. Microbiology of the ethmoid sinus is less well documented and presumably reflects that of the maxillary sinus. Cultures from HIV-positive patients do not yield organisms significantly different from those of non–HIV-infected patients.[11]

A culture and Gram stain are particularly important, since cultures of anaerobes can rarely be easily obtained in the office. Aspiration of purulent material and appropriate transport media help to ensure adequate culture to identify anaerobes. A Gram stain showing significant numbers of bacteria in the absence of routine aerobic growth would indicate anaerobic contamination. Modification of an ear suction with a secretion trap can be used specifically to sample individual sinus ostia to obtain material for culture and Gram stain under endoscopic control (see Figure).

TREATMENT

Antibiotics and Topical Steroids. Because of the microbiology described, antibiotics effective against a spectrum of anaerobes should be chosen for treatment of chronic sinusitis. While amoxicillin gives reasonably good coverage, addition of other antibiotics such as metronidazole or, in refractory cases, clindamycin, may be particularly useful. Since metronidazole has virtually no aerobic coverage, it must be used in combination with an antibiotic that provides such coverage, particularly of *Pneumococcus* and *Hemophilus.* Other antibiotics that have proven useful in combination, giving broad-spectrum coverage for both unusual aerobic organisms and anaerobic bacteria, include erythromycin and sulfamethoxazole-trimethoprim. Medication supplying erythromycin in combination with sulfisoxazole is available only in pediatric preparations. The combination of amoxicillin and clavulanate potassium (Augmentin) is a broad-spectrum agent effective against gram-negative and gram-positive bacteria. It has the advantage of activity against β-lactamase–producing organisms (eg, *H influenzae* and *S aureus*) as well as anaerobes. Cephalosporins that treat anaerobic infection and resistant *Hemophilus* may be useful both for penicillin-allergic patients and those who may be infected with *Staphylococcus* or penicillinase-producing *Hemophilus.* Cefuroxime axetil, with its twice-daily dosing, has an advantage over cefaclor, given three times a day, and has recently been proven efficacious in acute sinusitis. While antibiotics indicated for acute sinusitis are rarely also specifically approved for chronic sinusitis, the same principles of selection may be employed for both stages of the disease.

Resolution of chronic sinusitis involves not only reversal of the acute pathogenic bacterial growth, but reestablishment of mucociliary transport and resolution of edema of the sinus ostia. It is therefore unlikely that a simple 7- to 10-day course of antibiotics will be adequate, and a regimen of 3 to 4 weeks seems reasonable. Such prolonged therapy may prove invaluable, particularly for patients with unusual surgical risks, or in those who have had multiple procedures. All patients on such therapy, however, must be cautioned about the potential complications. Topical steroids may be particularly helpful if chronic edema accompanies sinusitis, or if allergic reactive airway disease is part of the underlying problem. Occasionally, systemic immune treatment is indicated, particularly for patients with nasal polyposis and allergy. Whenever possible, however, topical steroid application should be employed.

Surgery. The advent of routine radiographs to diagnose chronic maxillary sinusitis in the early part of this century led to a focus on maxillary sinusitis as a discrete entity. Surgery on the sinus focused on the Caldwell-Luc procedure, which did not address normal drainage patterns for the maxillary sinus. The recent advent of functional endoscopic sinus surgery has rekindled interest in the sinus endoscope, which first emerged at the turn of the century.[2-6,12]

Current surgical treatment of chronic sinusitis involves a number of approaches. It has been observed that sinuses that are aerated through inferior antrostomies still do not function normally; in the attempt to move mucus into normal ostia, the sinus continues to be obstructed in the ethmoidal ostiomeatal complex and cannot clear itself of disease. The patient therefore remains symptomatic. Similarly, simple trephination of the frontal sinus without removal of the obstruction in the frontal sinus recess, while helpful in relieving symptomatic pressure, seldom leads to prolonged improvement.

Ethmoidectomy improves the aeration of the sinuses and, more important, promotes normal mucociliary transport from the maxillary and frontal sinuses and the ethmoid into the nose. At least three different methods can be used. Intranasal ethmoidectomy, performed with a headlight or microscope, will improve drainage of the sinuses in many individuals; however, it does not provide the anatomic detail available with telescopes. Moreover, because of the inability to change the viewing angle, this procedure makes it virtually impossible to adequately dissect the frontal sinus recess.

Intranasal endoscopic ethmoidectomy can result in long-term restoration of sinus function. It has the advantage of allowing dissection of the frontal sinus recess and anterior ethmoid; however, it requires follow-up cleaning of the sinus to ensure that scar and/or granulation tissue do not result in sinus obstruction. The procedure is well tolerated under local anesthesia and allows an extra margin of safety. With a conscious patient, pain generated by the skull base or orbit can often alert the surgeon to their proximity, and possible endangerment to these structures can be avoided. The primary limitation to endoscopic ethmoidectomy is bleeding, since visualization of the discrete anatomy is essential. Techniques to minimize bleeding or to remove blood are particularly useful. There is no substitute for a coronal computed tomographic scan in appreciating the relationship between the skull base and superior ethmoid air cells.

The external ethmoidectomy remains the standard for relatively safe decompression of the ostiomeatal complex, since the orbit and skull base can be identified from external landmarks that remain visible during the procedure. The external ethmoidectomy primarily provides an advantage of safety to the orbit, as the periostium can be identified early in the procedure and followed back to the sphenoid itself if necessary. External ethmoidectomy is not as technically demanding as intranasal endoscopic ethmoidectomy, but makes it difficult to perform an adequate, frontal sinus recess, anterior ethmoidectomy because of the angle involved. Both approaches allow sphenoid sinusotomy as an extension of the procedure, and disease that extends to this sinus can easily be treated.

A simple endoscopic approach to the sphenoid sinus can usually be performed through the natural ostium itself when infection is limited to that area, but this is rarely the only sinus problem present.

SUMMARY

Successful management of both acute and chronic sinusitis requires an understanding of the microbiology and functional anatomy of the ostiomeatal complex of the anterior ethmoid and of the relationships between the anterior and posterior ethmoid, as well as the ethmoid and sphenoid areas. Drainage of the frontal sinus recess and maxillary ostia through the ethmoid highlights the significance of this anatomic area. Resolution of disease often leads to complete improvement of the patient. When isolated ethmoidal air cells remain obstructed or infected, the endoscopic approach can offer an advantage by allowing discrete dissection of these cells and keeping them open postoperatively. Increased awareness of these aspects of sinusitis on the part of the entire medical community could result in increased opportunities for proper diagnosis, management, and resolution of disease.

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ETIOLOGY AND MANAGEMENT OF PHARYNGITIS AND PHARYNGOTONSILLITIS IN CHILDREN: A CURRENT REVIEW

JACK L. PARADISE, MD
PITTSBURGH, PENNSYLVANIA

Although viruses are the most common causes of childhood throat infections, interest in the etiology of these infections has primarily focused on whether an individual episode is caused by group A β-hemolytic streptococcus (GABHS), particularly since the recent outbreaks of rheumatic fever in certain areas of the country. Penicillin remains the cornerstone of treatment in GABHS pharyngitis. Early treatment effects prompt clinical improvement and reduces the risk of transmission. Whether early treatment suppresses immunologic response and results in a higher recurrence rate than does delayed treatment is still unknown, but recent evidence suggests that it does not. The causes of persistent GABHS carriage, its clinical importance, and optimal methods of treatment are all still in question. When penicillin treatment does not eradicate carriage, other drugs may be efficacious. In children severely affected with recurrent throat infection, tonsillectomy is generally effective and is sometimes a desirable option.

KEY WORDS — pharyngitis, pharyngotonsillitis, streptococcal carriage, throat infection, tonsillitis.

ETIOLOGY

After the common cold and otitis media, acute throat infection, ie, pharyngitis and/or tonsillitis, is the most common illness diagnosed by US pediatricians.[1] The organisms that cause pharyngitis and pharyngotonsillitis episodes include not only viruses and bacteria, but also *Mycoplasma*, *Toxoplasma*, and *Candida* species.

A number of bacterial pathogens in addition to group A β-hemolytic streptococcus (GABHS) may cause pharyngitis. These include non–group A β-hemolytic streptococci[2,3]; *Corynebacterium diphtheriae*, which fortunately is now rare in the United States; *Corynebacterium hemolyticum*, an organism recently reported to cause pharyngitis — often associated with a scarlatiniform rash — primarily in older children and adults[4,5]; *Neisseria gonorrhoeae*, which may cause pharyngitis that is clinically indistinguishable from pharyngitis caused by other organisms[6]; and *Chlamydia trachomatis*, which causes pharyngitis primarily in young adults.[7] Whether *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Staphylococcus aureus*, or *Neisseria meningitidis* can cause pharyngitis is not clear.[8] Pharyngitis caused by *C hemolyticum* is easily confused clinically with scarlatina; since the former responds better to erythromycin than to penicillin, microbiologic differentiation is important.

Pharyngitis, generally without distinguishing clinical features, also may be caused by a variety of respiratory viruses, including adenovirus, parainfluenza virus, rhinovirus, herpes simplex, respiratory syncytial virus, Epstein-Barr virus, influenza virus, coxsackievirus A, coronavirus, and cytomegalovirus.

Perhaps the best study of the etiology of pharyngitis as encountered in practice is that reported by McMillan et al.[9] Two groups of patients from a private pediatric practice in Camillus, NY — 320 children and adolescents with pharyngitis and 308 asymptomatic controls — were studied from January to April 1985. Cultures were obtained for respiratory viruses, GABHS, *Mycoplasma pneumoniae*, and *C trachomatis*. Viruses were isolated on throat culture from 16.3% of the cases, compared with only 3% of the controls, and GABHS was isolated from 40.7% of the cases, compared with 11.7% of the controls. Non-group A streptococci were distributed among cases and controls about equally (2.5% versus 3.6%); the same was true of *M pneumoniae* (15.8% versus 17.6%). Two or three separate organisms were isolated from 10.6% of the cases, compared with only 1.9% of the controls. *Chlamydia trachomatis* was not isolated from any of the subjects. None of the organisms sought were isolated from 39.7% of the cases and 70.1% of the controls, although it seems possible that viruses might have been present, but not successfully isolated, in some of the children in both groups. In summary, whereas there were substantial differences overall between the flora in the two groups, there was enough overlap so that one could not infer from the throat culture alone whether an individual patient represented a case or a control.

The remainder of this paper will be devoted to a discussion of three important pharyngitis-related topics: the diagnosis and management of GABHS pharyngitis, the streptococcal carrier state, and the use of tonsillectomy for recurrent throat infection.

GABHS PHARYNGITIS

DIAGNOSIS

A number of clinical features are characteristic of

From the Ambulatory Care Center and Department of Pediatrics, Children's Hospital of Pittsburgh, and the Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. Supported in part by grant HD 07403 from the National Institutes of Health/National Institute of Child Health and Human Development.

REPRINTS — Jack L. Paradise, MD, Children's Hospital of Pittsburgh, One Children's Place, Pittsburgh, PA 15213-3417.

GABHS pharyngitis, including extreme throat discomfort, often accompanied by odynophagia; high fever; a scarlatiniform rash; pharyngeal exudate; petechiae on the soft palate; and tender anterior cervical lymphadenopathy. However, in atypical cases of GABHS pharyngitis none of these features may be present, and in non-GABHS pharyngitis any of them may be present. Streptococcal infection of the upper respiratory tract in infants and young children may be characterized by chronic rhinitis, accompanied by excoriation around the nares, cervical lymphadenopathy, and/or failure to thrive. This combination of findings has been termed streptococcosis. Symptoms and signs that should lead one to doubt the presence of GABHS infection, although none can rule it out, include acute coryza, hoarseness, and cough.

Interest has recently been accorded so-called rapid strep tests, which use one of a variety of methods of streptococcal antigen detection to indicate the presence of GABHS in the pharynx in a relatively short time. The test kits currently available commercially are of two types: those that employ the original latex agglutination test and those that employ the newer, solid-phase, enzyme immunoassay test. The various test kits differ in a number of performance features and have recently been reviewed critically by Radetsky et al.[10] As a group, these tests are highly specific but variably sensitive; none is satisfactory for conclusively ruling out the presence of GABHS infection. Accordingly, a backup culture is needed for all negative tests. Of the two types of rapid strep tests, a consensus appears to be emerging that the immunoassay test is preferable.[11]

TREATMENT

Early treatment of GABHS pharyngitis with an appropriate antimicrobial drug results in more rapid clinical improvement than delayed treatment or no treatment.[12-16] Treatment can prevent suppurative complications such as abscesses, cervical lymph node infections, and perhaps otitis media and sinusitis, even though those conditions are usually caused by organisms other than GABHS. Most important, timely treatment with penicillin can prevent the development of rheumatic fever[17] and probably, in some instances, glomerulonephritis.[18,19]

Treatment also may reduce the risk of recurrence. Finally, timely treatment can prevent transmission to others, which also may help minimize the enhancement of GABHS virulence and, in turn, perhaps reduce the capacity of the organism to cause rheumatic fever.[20]

Patient Selection. When a rapid strep test is positive in a child with pharyngitis, the decision to institute appropriate antimicrobial treatment is an easy one. However, if a rapid test is not available, or is negative, presence or absence of GABHS infection must be determined by a traditional culture. When the clinical features of an illness make it doubtful that the child has GABHS pharyngitis, one relies on the culture results to dictate treatment. However, when GABHS infection seems highly likely on the basis of presenting clinical features, one can follow any of a number of strategies with various costs, conveniences, and outcomes.[21] My own preference under such circumstances is to obtain a culture and begin treatment with penicillin promptly. If the culture is positive for GABHS, treatment is, of course, continued. If the culture is negative for GABHS and the patient is not markedly improved, treatment is discontinued. If the culture is negative but the patient is much improved after having received treatment, the improvement may have been spontaneous, or on the other hand may indicate that the culture was falsely negative[22,23] or that the infection was caused by a penicillin-sensitive organism other than GABHS. Under such circumstances, given the relatively low risk and low cost of penicillin treatment, I prefer to continue treatment for a total of 10 days.

Choice of Antimicrobial Drug. Indices of success or failure of treatment may be clinical, bacteriologic, or both, but most attention in the literature is devoted to so-called bacteriologic failure: the persistence or prompt recurrence of GABHS in the pharynx after antimicrobial treatment, often without regard to the presence or absence of accompanying symptoms. Various rates of bacteriologic failure following treatment with penicillin have been reported.[24-26]

In an attempt to improve both bacterial and clinical cure rates, Chaudhary et al[27] randomly assigned 79 children with pharyngitis and a positive GABHS culture to receive either penicillin alone for 10 days or penicillin for 10 days with rifampin added during the last 4 days of treatment. At the first follow-up visit, 4 to 7 days after completing treatment, all of the 40 children in the penicillin-rifampin group were culture-negative and symptom-free, while 11 of 39 children in the penicillin-only group were culture-positive, and 8 of the 11 had symptoms of pharyngitis. All 8 responded clinically and bacteriologically to subsequent treatment with penicillin plus rifampin, although the 3 who were culture-positive but clinically well remained culture-positive after this retreatment. At the second follow-up visit, 18 to 30 days after the original course of treatment had been completed, 6 children who had been clinically and bacteriologically cured at the first follow-up visit — 1 in the penicillin-only group and 5 in the penicillin-rifampin group — were again culture-positive and symptomatic.

Thus, while the addition of rifampin appeared to yield better early results, longer-term results were not strikingly better with the combined treatment than with penicillin alone. It is possible that results may have been confounded because of inequalities between the two treatment groups in the number of children who had been GABHS carriers, since the report did not state whether children had been so identified. (The issue of carriage is discussed further on.)

Instances of bacteriologic or clinical failure notwithstanding, no drug has proven superior to penicillin for the routine treatment of GABHS throat infection, and on the grounds of efficacy, safety, and cost, penicillin remains the drug of choice. Even in patients with bacteriologic failure, the GABHS isolates recovered have been found highly sensitive to penicillin in vitro.[26] In children allergic or thought to be allergic to penicillin, erythromycin is probably the best drug to use. Cephalosporins also might be used, although there is a chance of cross-reactivity if the child is truly penicillin-allergic. Neither tetracyclines nor the sulfonamides are satisfactory substitutes for penicillin in treating GABHS infection.[28]

Route of Administration and Dosage of Penicillin. Penicillin may be administered in a variety of forms. In one form, benzathine penicillin G alone or in combination with procaine penicillin G is given in a single intramuscular dose, with dosage depending on the age and size of the child. A more common regimen is oral phenoxymethyl penicillin (penicillin V) administered three or four times daily for a 10-day period.

The advantages of intramuscular administration are that one need not worry about compliance, and that treatment is completed in one simple step. Of the disadvantages, the most prominent is pain; benzathine penicillin is particularly irritating, with pain and tenderness remaining at the injection site for an extended period, even with the addition of procaine penicillin. There is also an increased risk of sensitizing the patient, especially with procaine penicillin. Finally, the risk of anaphylaxis is greater with intramuscular than with oral administration.

Weighing these advantages and disadvantages, I conclude that oral treatment is preferable to intramuscular treatment under most circumstances in the population of children I encounter. However, intramuscular treatment should be considered 1) if the patient is very ill, vomiting, or not able to tolerate oral medication; 2) if compliance with an oral regimen seems doubtful, on the basis of assessment of family organization and resources; or 3) if the child has had frequent recurrence of GABHS episodes despite seemingly adequate oral penicillin treatment. Finally, for a child with rheumatic heart disease, in whom it is essential to minimize the risk of persistent GABHS infection, intramuscular penicillin administration is probably prudent.

The standard dosage regimen for oral penicillin V is 250 mg three or four times daily, regardless of age. Twice-daily administration may or may not be effective,[29] but evidence suggests that 750 mg once daily is not satisfactory.[30] Neither is treating GABHS infection for fewer than 10 days.[31] Given the ever-present risk of inadequate compliance, I routinely recommend that penicillin be given four times daily, with the hope that parents will administer the drug a minimum of two or three times daily over the 10-day period.

Early Versus Delayed Treatment. An old issue of renewed concern is whether to start oral penicillin treatment immediately — a practice that may have become more common since the advent of the rapid strep test. The potential advantage of immediate treatment is more prompt clinical improvement. The disadvantage is that early treatment may interfere with the body's natural immune response, heightening the likelihood of early recurrence.

Pichichero et al[15] reported a study in which clinical responses and rates of relapse and recurrence were compared in two groups of children with GABHS pharyngitis. One group, comprising 59 children, received relatively immediate treatment with oral penicillin; in the other group, of 55 children, treatment was delayed for about 2 days. Relapse rates in the two groups were similar: 17% in the early-treatment group and 15% in the delayed-treatment group. Recurrence within 3 to 7 weeks was almost twice as high in the early-treatment group (24%) as in the delayed-treatment group (15%), but the difference was not statistically significant. On the other hand, recurrence from 8 weeks to 20 weeks after initial infection was 14% in the early-treatment group, compared with 2% in the delayed-treatment group — a difference that was statistically significant ($p = .04$). The authors concluded that early treatment had indeed interfered with their subjects' immune responses. Despite the finding of more prompt clinical improvement in the subjects who received early treatment, they recommended that under most circumstances antibiotic treatment for GABHS pharyngitis be postponed for 48 hours.[32]

A primary limitation of this study is that serologic typing of the streptococcal organisms recovered was not performed, so that it is not known whether recurrences were due to the same organisms that caused the original episodes.[33] This limitation was addressed in a recent, similarly designed study by Gerber et al[34] in which serotyping of all GABHS isolates was performed. In this study, no significant differences were found between the immediate-treatment group and the delayed-treatment group, whether in the proportion of subjects who had homologous GABHS serotypes isolated on follow-up, in the proportion who had heterologous serotypes isolated, or in the proportion whose positive cultures were associated with symptomatic episodes of pharyngitis. These findings cast considerable doubt on the possibility that immediate treatment has any clinically important adverse effect and support the advisability, for the reasons noted earlier, of treating promptly once GABHS infection has been documented.

STREPTOCOCCAL CARRIER STATE

DEFINITION AND DIAGNOSIS

The term streptococcal carrier has traditionally been applied to patients with either of two distinct clinical conditions: in the one case, the child does not have pharyngitis and is not ill, but has a positive throat culture for GABHS; in the other case, the child has pharyngitis and a positive culture, but does not develop a serologic response, and on that basis is not believed to have an actual streptococcal infection. It is important to know which of these two conditions is being referred to when the term streptococcal carrier is used.

That the presence or absence of an antibody response may not effectively distinguish whether GABHS infection has actually occurred is suggested by the results of a study recently reported by Gerber et al.[35] In this study of a group of children with pharyngitis and positive cultures for GABHS, but with no rise in streptococcal antibody titers, the clinical response was much better in a subgroup who received penicillin than in a subgroup who received placebo. It thus appears that whether a child with pharyngitis and a positive GABHS culture truly has a GABHS infection or is a GABHS carrier who happened to develop viral pharyngitis cannot be distinguished with certainty.

Under these circumstances, and particularly because of recent concern regarding resurgence of rheumatic fever,[36,37] it would seem prudent to administer a full course of appropriate antibiotic treatment to every child who has both pharyngitis and a positive culture for GABHS.

Several recent reports have called attention to an apparent secular increase in rates of pharyngeal GABHS positivity persisting after a presumably adequate course of antimicrobial treatment for GABHS-associated pharyngitis.[24,25,27,38,39] One possible explanation is inadequate compliance: that children simply had not received penicillin in the recommended dosage for the full 10-day period. (Even the presence of penicillin in the urine would not confirm adequate dosage.) Another possibility is that β-lactamase–producing organisms concurrently present in the pharynx had inactivated the administered penicillin. A third possible explanation is the development of bacterial resistance, but studies of that issue do not suggest that streptococcal resistance to penicillin is developing.[39,40] Finally, other, unknown factors, perhaps intrinsic to the host, may have been operative.

ERADICATION OF ASYMPTOMATIC CARRIAGE

A number of reasons might be advanced for eradicating GABHS carriage. In children with recurrent episodes of GABHS-positive throat infection it sometimes remains uncertain whether episodes are due to GABHS infection or to viral infection superimposed on the GABHS carrier state. The ease with which eradication can be accomplished and, when it is accomplished, the timing of GABHS reappearance relative to subsequent pharyngitis episodes may help differentiate GABHS-induced infection from non–GABHS-induced infection.

It also is possible that eradicating GABHS carriage may reduce rates of infection recurrence. Certain studies[41,42] have suggested that children who have recurrent GABHS throat infection and persistent GABHS carriage after recovery from individual episodes might have fewer subsequent recurrences if carriage could be eradicated. Validation or disproval of this hypothesis is important.

Another reason to eradicate GABHS carriage might be to reduce spread of the organism to other individuals. Evidence suggests, however, that the risk of spread from carriers as compared with that from children with actual GABHS infection is low.[43]

Finally, one might wish to eliminate asymptomatic GABHS carriage in the hope of reducing the risk of rheumatic fever, since in recent outbreaks of rheumatic fever many children had no discernible sore throat symptoms.[36,37] Again, however, available evidence suggests that in GABHS carriers the risk of developing rheumatic fever is low.[43]

It thus appears that eradication of GABHS carriage might be desirable in two groups of children particularly — those with recurrent GABHS-positive episodes of pharyngitis, and those who have a history of rheumatic fever or a family member with such a history — in the interest of minimizing not only risk but also anxiety.

Three studies in which attempts were made to eliminate GABHS carriage by medical means have been reported. Tanz et al[40] studied a group of children defined as carriers because 3 weeks after having received intramuscular benzathine penicillin — in some cases because of GABHS pharyngitis and in other cases because repeated throat cultures had been persistently GABHS-positive — they were asymptomatic but their throat cultures were still GABHS-positive. Subjects were randomly assigned to one of three groups: one group received no treatment, a second group received a second injection of benzathine penicillin, and a third group received benzathine penicillin with the addition of oral rifampin. Three to 5 weeks after treatment, GABHS eradication rates were 23%, 30%, and 93%, respectively. The eradication rate in the third group remained high for up to 12 weeks. Combination therapy thus appeared to be a highly effective method for eradicating GABHS carriage, at least for a relatively short term. One must recall, however, that in a study referred to earlier involving children with

GABHS-positive pharyngitis, late results from using oral penicillin plus rifampin were less uniformly favorable.[27]

In a second study, by Brook and Hirokawa,[42] subjects were children and young adults who were GABHS carriers and had histories of at least three documented episodes of GABHS throat infection during each of the 2 preceding years. They were randomly assigned to receive a 10-day course of penicillin, erythromycin, or clindamycin. Ten days after completing treatment, only 1 of 15 subjects in the clindamycin group, compared with 13 of 15 in the penicillin group and 9 of 15 in the erythromycin group, had a positive GABHS culture. At follow-up 1 year later, only 1 episode of tonsillitis had occurred in the 15 subjects originally treated with clindamycin, compared with 27 episodes in 14 penicillin-treated subjects and 15 episodes in 14 erythromycin-treated subjects. It was not stated whether this final tally was based on inquiry at follow-up or on prospective monitoring.

Most recently, Kaplan and Johnson[44] studied 45 children who were defined as pharyngeal GABHS carriers because after 10 days of treatment with penicillin V they had the same GABHS serotype as before treatment. The children were assigned alternately to receive either a second 10-day course of penicillin V or a 10-day course of amoxicillin–clavulanate potassium. Throat cultures remained GABHS-positive in 17 of the 24 children who had penicillin V retreatment. When those 17 were then treated with amoxicillin–clavulanate potassium, only 3 remained culture-positive. In contrast, of the 21 children assigned originally to receive amoxicillin–clavulanate potassium, only 2 remained GABHS-positive after treatment. Both then received a second course of penicillin V and 1 of the 2 became culture-negative. It should be noted that considerably less dramatic results than with amoxicillin–clavulanate potassium had been previously obtained with dicloxacillin in a similar study reported from the same laboratory.[39]

One might infer that the promising effects in eradicating GABHS carriage seen with rifampin (in association with penicillin), clindamycin, and amoxicillin–clavulanate potassium are related to the shared ability of the drugs to eradicate normal pharyngeal flora that produce β-lactamase, thereby preventing inactivation of penicillin by this enzyme. However, a recent study in children who had GABHS-positive pharyngitis but were not carriers suggests that bacteriologic treatment failure may be a function of factors other than the presence or absence of β-lactamase–producing organisms.[45]

Reported studies have all been relatively short-term, and it is possible that all of these drugs succeed in suppressing the carrier state only temporarily. Long-term studies would therefore be quite valuable.

Follow-up Throat Cultures. A follow-up throat culture is unnecessary in a child with only sporadic episodes of GABHS pharyngitis who recovers uneventfully with antimicrobial treatment, since a positive culture would not in itself constitute justification for further treatment and might serve as a source of unnecessary anxiety.

On the other hand, with a second episode of GABHS pharyngitis within a 6-week period, a follow-up culture would be advisable 3 to 10 days after treatment is completed. A positive culture would raise the possibility of treatment noncompliance, infection that had not been completely eradicated, or a child who was a GABHS carrier. Retreatment with oral penicillin at twice the usual dosage or for twice the usual duration could be tried, or an injection of intramuscular benzathine penicillin might be appropriate.

If a culture was again positive, an attempt to eradicate GABHS carriage using amoxicillin–clavulanate potassium, penicillin plus rifampin, or clindamycin would be justified.

TONSILLECTOMY

When episodes of tonsillitis or pharyngotonsillitis have recurred with disturbing frequency, whether or not they have been due to GABHS, the option of tonsillectomy may be considered. This procedure has long been controversial, largely because evidence has been inadequate either for or against its success in children with various clinical presentations.[46] We are currently completing the third of three clinical trials examining the efficacy of tonsillectomy in children with recurrent throat infection. The first two trials were conducted in parallel and were identical in design except that assignment to surgical or control status was made randomly in one of the trials and according to parental preference in the other.[47] Criteria for entry were stringent: seven episodes of throat infection in 1 year, five in each of 2 years, or three in each of 3 years, with various additional requirements relating to clinical features and documentation of these episodes.

Of 187 children meeting our criteria, 91 were enrolled in the randomized trial and 96 in the nonrandomized trial. In each trial, outcomes in the tonsillectomy group were consistently more favorable than in the control group over a 3-year period, particularly with regard to moderate or severe episodes of throat infection. For example, in the randomized trial, of the children completing the first year of follow-up, 92% of tonsillectomy subjects had no moderate or severe episodes, compared with 34% of controls. One third of the children originally assigned to control status were eventually withdrawn to receive tonsillectomy, but of those who were not, most had relatively mild courses of illness. Complications, all readily managed or self-limiting, developed in 14% of the subjects who received tonsillectomy.

We concluded that these results warranted the election of tonsillectomy for children meeting our eligibility criteria, but also provided support for nonsurgical management. Factors that might influence a decision include the level of parental concern about the risk of rare, severe complications; parents' and children's wishes; family tolerance of illness; the degree to which other family stresses are operative; the child's school performance; accessibility and quality of health-care services, including anesthetic and surgical service and facilities; financial considerations; and the child's tolerance of antimicrobial drugs.

These findings cannot properly be extrapolated to less severely affected children. Our third clinical trial, which examines the efficacy of tonsillectomy in children somewhat less severely affected with recurrent throat infection than those in the first two trials, should help us arrive at recommendations for appropriate illness criteria to use in deciding between surgical and nonsurgical management.

ANTIMICROBIAL PROPHYLAXIS

An alternative to tonsillectomy worth considering is antimicrobial prophylaxis. In patients with rheumatic fever, this approach was long ago shown to be effective in preventing recurrent GABHS infection and, in turn, recurrent rheumatic episodes.[48,49] There is little evidence, however, of the general efficacy of prophylaxis in preventing recurrent throat infection in children. Two early, controlled, nonblinded trials found prophylaxis with penicillin effective in reducing the recurrence rate of respiratory illnesses of unspecified nature,[50,51] and one double-blind, placebo-controlled crossover trial found a sulfonamide effective in reducing recurrences of acute tonsillitis specifically.[52] A later, similar trial with penicillin was not completed successfully, but gave suggestively favorable results.[53] Clearly, the efficacy of prophylaxis deserves further study. In the meantime, in the child with troublesome recurrent throat infection, a trial of antimicrobial prophylaxis would appear a worthwhile first strategy before contemplating tonsillectomy.

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CURRENT INDICATIONS FOR TONSILLECTOMY AND ADENOIDECTOMY

CHARLES D. BLUESTONE, MD
PITTSBURGH, PENNSYLVANIA

Tonsillectomy and adenoidectomy are currently the most common pediatric surgical procedures performed in the United States. Tonsillectomy may be effective in recurrent acute throat infection (acute tonsillitis), chronic tonsillitis, tonsillar hypertrophy, and peritonsillar abscess. Antimicrobial therapy may also be beneficial. Clinical trials evaluating children with obstructive adenoids are currently being evaluated; anecdotal evidence points to improvement in development and quality of life after surgery. The efficacy of adenoidectomy in paranasal sinusitis has not been evaluated in clinical trials; antimicrobial therapy or the possibility of upper respiratory tract allergy should be considered in such cases. For acute otitis media, recommendations range from no treatment in cases that will abate with time, to antimicrobial prophylaxis, to myringotomy with tympanostomy tube insertion, adenoidectomy with or without tonsillectomy, or a combination of adenoidectomy with myringotomy and/or tympanostomy tubes. The decision for or against otic and/or pharyngeal surgery should be individualized on the basis of severity, duration, and frequency of illness; previous treatment; and risk.

KEY WORDS — adenoidectomy, myringotomy, otitis media, recurrent throat infection, tonsillectomy.

INTRODUCTION

An estimated quarter of a million tonsillectomies and adenoidectomies are performed annually in the United States.[1] The actual number is undoubtedly somewhat higher, since many of these procedures are done on an outpatient basis, and precise retrieval of data is difficult. Although tonsillectomy and adenoidectomy are currently the most common major pediatric operations performed, their use has steadily declined during the past 20 years from an annual high of 1 million. This decrease has been attributed to many factors, not the least of which is the concern regarding a lack of convincing evidence from randomized clinical trials showing that the procedures are effective in the management of either recurrent throat infection or otitis media (OM), two common conditions for which these operations are recommended. However, results of recent trials are now available to guide both clinicians and parents in deciding who might benefit from these procedures.

In this paper I briefly describe assessment and management of the conditions for which tonsillectomy and/or adenoidectomy are frequently considered, results of studies that show the success or failure of these procedures, and the criteria for surgery. I also give my recommendations regarding use of these procedures for indications that have not been adequately evaluated in clinical trials. Since myringotomy with or without tympanostomy tube insertion is frequently recommended as an alternative or companion procedure to adenoidectomy for treatment of OM, I include a discussion of these procedures as well.

TONSILLECTOMY

DEFINITE INDICATIONS

Awareness that there are definite, as opposed to elective, indications for tonsillectomy and adenoidectomy has increased over the past two decades.[2] Infants and children who have obstructive tonsils and/or adenoids that cause obstructive sleep apnea or cor pulmonale should have these structures removed.[3-7] For these indications, I prefer the term obstructive tonsils and adenoids, as opposed to hypertrophy, since the degree of obstruction is related to the size of these structures within the space and configuration of the pharynx of an individual patient. In addition, the obstruction is frequently dynamic, in that its degree can change with body position and sleep; obstruction is usually most pronounced when the individual is recumbent and during sleep, when the tonsils can prolapse and the surrounding tissues of the pharynx are most compliant.

Obstructive tonsils that are unresponsive to antimicrobial therapy and that cause failure to thrive or progressive weight loss due to marked swallowing impairment should be removed. In addition, tonsillectomy is indicated for excisional biopsy for the relatively rare case in which malignancy of the tonsil is suspected, or for persistent or recurrent tonsillar hemorrhage, either associated with acute pharyngotonsillitis or due to severe tonsillar hypertrophy that is unresponsive to treatment of the underlying infection. Some authorities would add chronic fetor oris secondary to retention of debris within the tonsillar crypts to the list of definite indications. However, I believe this tends more toward

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From the University of Pittsburgh School of Medicine and the Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania.

REPRINTS — Charles D. Bluestone, MD, Dept of Pediatric Otolaryngology, Children's Hospital of Pittsburgh, One Children's Place, 3705 Fifth Ave at DeSoto St, Pittsburgh, PA 15213.

an elective indication, since most patients with this complaint, usually teenagers, can be treated by nonsurgical means.

Assessment. Assessment of upper airway obstruction due to obstructive tonsils and adenoids should include the following.

1. A history should be taken of snoring, sleep pauses or apnea, mouth breathing, and daytime somnolence.

2. Physical examination should include observation for a lack of lip seal, mouth breathing, hyponasality, and distortion of speech, such as a hot potato voice. In extreme cases, evidence of congestive heart failure may be found. Examination of the intranasal cavity or postnasal space by either direct or indirect rhinoscopy may reveal nasal obstruction secondary to obstructive adenoids. A flexible fiberoptic endoscope may be helpful in evaluating the degree of obstruction.

3. Radiographs may be desirable in the child who is difficult to examine. A lateral soft tissue x-ray film of the head and neck can be useful for documentation and to determine the degree of nasal obstruction due to obstructive adenoids.

4. A formal sleep study may be indicated in children who have a history of sleep disturbance and whose parents are uncertain whether the child has sleep pauses or true sleep apnea. In most cases such a study is not feasible; as an alternative, parents can make a 5- to 10-minute audiotape of the child's sleep on two consecutive nights.[8] The recording should reveal whether the child snores while sleeping and, if so, whether there are sleep pauses or apneic episodes.

Development of cardiorespiratory complications in children with respiratory obstruction due to obstructive tonsils and/or adenoids may be related to susceptibility of the pulmonary vasculature, craniofacial malformation (such as occurs in Down's syndrome), obesity (eg, Pickwickian syndrome), preexisting congenital heart disease, abnormal pharyngeal musculature, or concurrent upper respiratory tract infection.

Choice of Procedure. When a diagnosis of severe airway obstruction is confirmed and the patient has either sleep apnea or evidence of alveolar hypoventilation, with or without cor pulmonale, a combination of tonsillectomy and adenoidectomy is usually indicated. On occasion, the adenoids may completely obstruct the nasopharyngeal airway, but the tonsils may be relatively small. Conversely, the tonsils may obstruct the airway in association with small adenoids. In such cases, either a tonsillectomy or adenoidectomy will suffice.[9] Both the adenoids and tonsils are involved in most patients with airway obstruction, however. The decision to perform only one procedure should be based on clear-cut evidence, and if there is any doubt whether the second procedure can be omitted, both tonsils and adenoids should be removed. A great deal of information is available regarding the pathophysiology of upper respiratory tract obstruction secondary to obstructive tonsils and adenoids. More research is needed, however, especially in cases in which the signs and symptoms of severe airway obstruction are lacking.

TABLE 1. EFFICACY OF TONSILLECTOMY FOR PREVENTION OF RECURRENT THROAT INFECTION

Follow-up Year	*Treatment Group*	*No. of Subjects*	*Episodes Per Subject* *Mean*	*Range*	*p**
First	Tonsillectomy	38	1.24	0-8	.001
	Control	35	3.09	0-10	
Second	Tonsillectomy	31	1.61	0-10	.001
	Control	29	2.66	0-7	
Third	Tonsillectomy	22	1.77	0-6	NS
	Control	20	2.20	0-6	

Modified from Paradise et al.[10]
NS — not significant.
*χ^2 test.

ELECTIVE INDICATIONS

Since most tonsillectomies and adenoidectomies are recommended on an elective basis, it is important to know under which circumstances such a course is most appropriate. The most common conditions for which elective tonsillectomy is indicated are frequently recurrent acute throat infection (acute tonsillitis), chronic tonsillitis, obstructive tonsils, and peritonsillar abscess. Only the first of these, recurrent throat infection, has been studied in a randomized clinical trial.

Recurrent Acute Throat Infection. In 1984, Paradise et al[10] reported the results of a randomized clinical trial involving 187 children severely affected by recurrent throat infection. (See Etiology and Management of Pharyngitis and Pharyngotonsillitis in Children, p 51.) Subjects were eligible only if episodes met strict criteria, including the number and frequency of episodes. Children with undocumented episodes were followed up to determine if they truly had tonsillitis; as had been reported earlier by Paradise et al,[11] many children did not have episodes of the frequency or severity described by their parents.

In children randomly assigned to either surgery (tonsillectomy) or nonsurgery (control) groups, tonsillectomy was shown effective in reducing the number of episodes of sore throat during the first and second years of follow-up, including episodes due to group A β-hemolytic streptococcus (GABHS; Table 1[10]). Third-year outcomes were also better in the surgical group, but the differences were not statistically significant. Similar outcomes were seen in children assigned to surgical or nonsurgical groups nonrandomly, ie, according to their parents' wishes. The investigators concluded that elective tonsillectomy is a reasonable alternative to medical treatment for cases of throat infection meeting the stringent criteria of the study. A clinical trial by Paradise et al of the efficacy of tonsillitis in less severe cases of throat infection has been completed and is presently being analyzed.

There has been increasing interest in the microbiology of recurrent tonsillitis, and in whether bacteria found in the core of the tonsils, aside from the presumed pathogen, are involved in the inflammatory process. In a study by Kielmovitch et al,[12] polymicrobial organisms were found in the core of the tonsils of children with recurrent tonsillitis and also those who had obstructive tonsils. Prevalence of *Streptococcus pyogenes* as well as β-lactamase–producing aerobic and anaerobic organisms was noticeable in both groups. From this study we, as have others, speculated that the high number of S *pyogenes* organisms in the core of the tonsils could have resulted in a persistent streptococcal infection due to the passive pathogenicity of the other, β-lactamase–producing, bacteria found in the core of the tonsils. These other bacteria may not be pathogenic, but since they can produce free β-lactamase, the therapeutic activity of penicillin may be impaired when S *pyogenes* is the causative organism. More recently, Brook and Foote[13] reported that children who lacked signs and symptoms of airway obstruction and acute or chronic infection also had polymicrobial bacteria in the core of their tonsils, although the number of bacteria was less than that found in children who had had recurrent infection.

Several investigators have speculated that recurrent acute tonsillitis may be more effectively treated with a β-lactamase–stable or β-lactamase–inhibiting antimicrobial agent to eradicate an underlying streptococcal infection. To date, there is no convincing evidence to substantiate this idea. Brook and Hirokawa[14] compared penicillin, erythromycin, and clindamycin in 45 patients with a history of recurrent GABHS infections. After a 1-year follow-up, there was less recurrent tonsillitis in the group treated with clindamycin than that treated with penicillin. (See Etiology and Management of Pharyngitis and Pharyngotonsillitis in Children, p 51.)

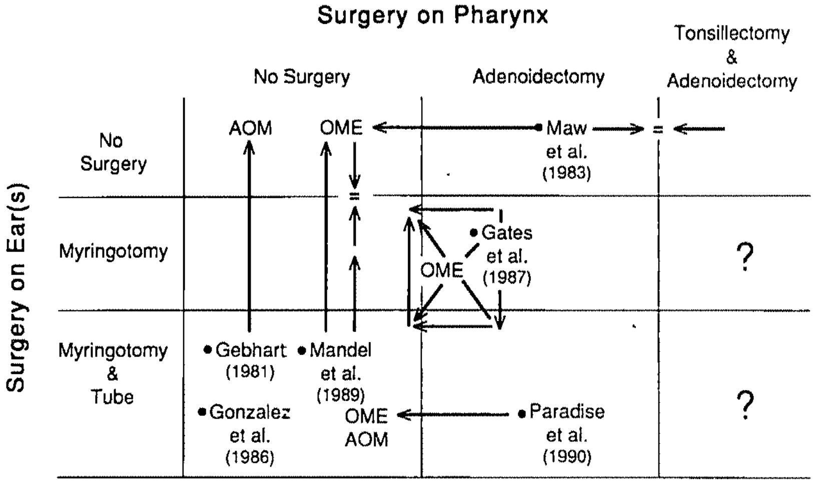
The decision for or against surgical intervention in patients with recurrent acute tonsillitis should be individualized. The outcome of the trial by Paradise et al[10] described earlier indicates that the clinician should assess the frequency, severity, and duration of episodes, along with the patient's disability, such as days lost from school. Documentation of episodes is imperative, as is determination of the presence of characteristic features such as tonsillar exudate, fever, cervical lymphadenopathy, cultures positive for GABHS, and failure of appropriate and adequate antimicrobial therapy.

Chronic Tonsillitis, Obstructive Tonsils, and Peritonsillar Abscess. Many patients, usually teenagers and young adults, who have chronic throat infection (which is thought to be due to chronic tonsillitis) frequently also have recurrent acute infection of the tonsils superimposed on the chronic condition. In these patients, management as described above probably is appropriate. Tonsillectomy may be of benefit, although there are no clinical trials of such cases to guide the physician in a decision for surgery. The physician should attempt to rule out other causes such as paranasal sinusitis, upper respiratory tract allergy, and chemical irritants (eg, smoking). If there is evidence of tonsillar infection but no cause has been found and treatment with penicillin has not been effective, a course of a β-lactamase–stable or β-lactamase–inhibiting antimicrobial agent might be considered, although the benefit of therapy with any antimicrobial agent remains to be proven.

For patients who have obstructive tonsils with or without hypertrophy and without obstructive sleep apnea or cor pulmonale, the duration of the obstruction should be long enough and sufficiently severe to warrant surgical intervention. Features such as snoring should be present. For patients whose obstruction is caused by hypertrophy of the tonsils, antimicrobial treatment may be tried in an effort to reduce the size of the tonsils and determine if there is subclinical infection. In the study by Kielmovitch et al[12] cited previously, S *pyogenes* was found in about one fourth of patients who had obstructive tonsils and who had not been treated previously. Since β-lactamase–producing organisms in the core of such tonsils may be involved in the pathologic process, a β-lactamase–stable or β-lactamase–inhibiting agent may be more effective for therapy than penicillin alone. Again, however, no evidence from clinical trials is available at present to support this method of treatment.

Although peritonsillar abscess as an indication for tonsillectomy also has not been evaluated by prospective randomized clinical trial, a decision for or against tonsillectomy may be straightforward at the two extremes of the disease spectrum. For example, a teenager with no previous episodes of throat infection and peritonsillar abscess who will allow incision and drainage or needle aspiration can probably be successfully treated on an outpatient basis with topical or local anesthetic. Recurrence rates in these cases are relatively low. Some clinicians advocate interval tonsillectomy. On the other hand, when a peritonsillar abscess develops in a young child who has had frequent recurrences of acute tonsillitis during the preceding 1 or 2 years, incision and drainage using topical or local anesthesia is usually not feasible. Incision and drainage or needle aspiration should be done in the operating room, at which time a tonsillectomy can be performed. For cases

Fig 1. Three-by-three table showing results of randomized clinical trials of most common surgical procedures for treatment or prevention of recurrent acute otitis media (AOM) and chronic otitis media with effusion (OME). Each block represents 1) surgery on ear or pharynx, 2) surgery on both, or 3) no surgery. Direction of arrows indicates which surgical procedures were reported as being more effective than other procedures or no surgery. Equal sign indicates that no significant differences were found between two procedures or combination of procedures. Question marks indicate lack of sufficient data. (Reproduced with permission from Bluestone CD. Indications for tonsillectomy, adenoidectomy and tympanostomy tube insertion: results of randomized clinical trials as applied to clinical practice. In: Myers EN, Bluestone CD, Brackmann DE, Krause CJ, eds. Advances in otolaryngology–head and neck surgery. Vol 5. St Louis, Mo: Mosby Yearbook, 1991:201.



that fall between these two extremes, physicians must use their best judgment until we have clinical trials evaluating the risks and benefits of tonsillectomy for peritonsillar abscess.

ADENOIDECTOMY WITH OR WITHOUT MYRINGOTOMY AND/OR TYMPANOSTOMY TUBE INSERTION

ELECTIVE INDICATIONS

Adenoidectomy is commonly recommended for four conditions: obstructive adenoids, recurrent or chronic adenoiditis, recurrent or chronic sinusitis, and prevention of recurrent or chronic OM. Of these, only recurrent or chronic OM has been evaluated in randomized clinical trials.

Obstructive Adenoids and Adenoiditis. At the Children's Hospital of Pittsburgh, Paradise et al have conducted a randomized clinical trial evaluating adenoidectomy for patients with obstructive adenoids. Although their results are not yet available, one can speculate that for the child who has moderate to severe nasal obstruction secondary to obstructive adenoids, adenoidectomy should reduce morbidity, including mouth breathing, snoring, and hyponasality. In the absence of sleep apnea or alveolar hypoventilation resulting in cor pulmonale, however, the operation still remains of uncertain benefit.[15] The question then becomes one of quality of life; improvement in the nasal airway, for example, has been shown to improve olfaction[16] and may help prevent or reverse abnormalities of dentofacial morphology.[17] In addition, adenoidectomy may correct hyponasal speech caused by nasal obstruction. Some clinicians and parents also believe that growth and development improves following relief of complete nasal obstruction in children with obstructive adenoids, possibly because of improved olfaction.

Until the Pittsburgh study is fully evaluated and reported, the clinician assessing a child with lack of lip seal, hyponasality, and snoring at night due to moderate to severe nasal obstruction should determine the obstruction's duration and severity and decide whether the child truly has nighttime respiratory obstruction. As previously described, an audiotape can be used to document this, and a lateral soft tissue x-ray film of the head and neck can help determine the degree of adenoid obstruction.

Little information is currently available about the epidemiology, natural history, and etiology of adenoiditis. However, a child with obstructive adenoids — especially when they are hypertrophic — may have chronic adenoiditis, and a course of antimicrobial therapy may reduce the hypertrophy and degree of nasal obstruction. There are no studies at present, however, that support the routine use of such agents for chronic adenoiditis.

Upper respiratory tract allergy may also cause obstructive adenoids, and this possibility should be investigated for a child with a history or signs and symptoms of upper respiratory tract allergy. It seems reasonable at this time to recommend adenoidectomy for children with moderate to severe nasal obstruction that is due to adenoid infection and is unresponsive to medical management. Again, this is a quality-of-life issue.

Paranasal Sinusitis. The benefit of adenoidectomy for children with frequently recurrent acute or chronic paranasal sinusitis remains uncertain; there have been no randomized clinical trials demonstrating that adenoidectomy is effective in reducing sinusitis morbidity. In a child with moderate to severe nasal obstruction secondary to obstructive adenoids, however, surgery to improve the nasal airway should be considered. As previously described, duration and severity of the obstruction should be assessed and clinical and radiographic evidence obtained. Antimicrobial therapy would be indicated in such cases, since adenoiditis may be causing the obstruction. The possibility of upper respiratory tract allergy and treatment with systemic antihistamines, immunotherapy, allergy control, or topical nasal preparations should be considered.

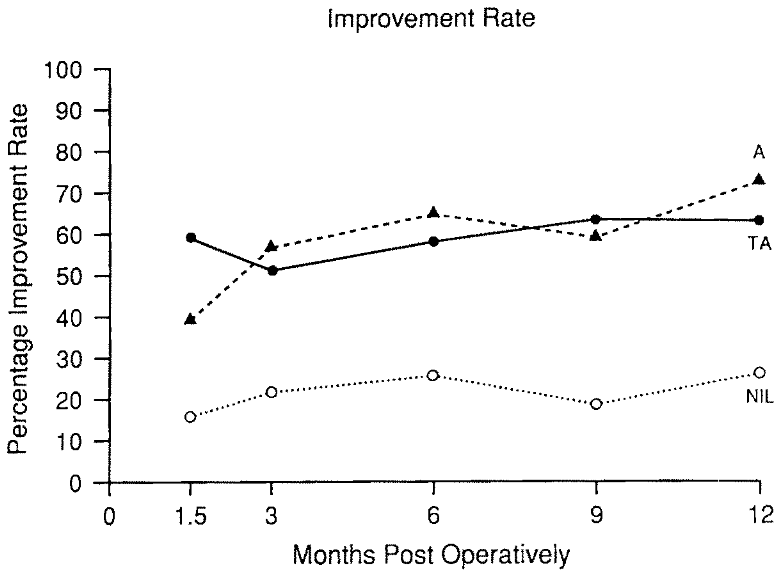


Fig 2. Improvement rate of middle ear effusion after adenoidectomy (A), tonsillectomy and adenoidectomy (TA), and no surgery (NIL). (Reproduced with permission.[23])

Otitis Media. Otitis media is the most common diagnosis made by pediatric physicians. In a prospective study of 498 children followed from birth to 7 years of age, Teele et al[18] found that the mean number of episodes of OM in the first year of life was 1.2, and that 17% of children had three or more episodes. For the following 6 years of life, about 75% had at least one episode.

My management recommendations for acute OM and OM with effusion have been fully described elsewhere,[19] but I present here a method for evaluating a child who may benefit from adenoidectomy in the management of OM. Since myringotomy with or without tympanostomy tube insertion can also be recommended for OM, either alone or in conjunction with adenoidectomy, I include a rationale for use of these procedures.

In Fig 1,[20-25] each of the nine blocks represents a treatment option. Randomized clinical trials by Gebhart[20] and Gonzales et al[21] demonstrated that myringotomy with tympanostomy tube insertion was more effective than no surgery in preventing recurrent acute OM in "otitis prone" infants. Figure 1 shows the efficacy of tubes over no tubes.

Antimicrobial prophylaxis is also effective against recurrent acute OM in this age group.[26,27] The physician could recommend no prophylaxis if episodes are not frequent, since episodes will probably abate naturally with age.[18] If prevention is desirable, a 6- to 8-week trial of an antimicrobial such as amoxicillin (20 mg/kg per day) is often effective, and then the prophylaxis can be continued for another 3 to 6 months, or until the next warm season. When such a trial fails, tympanostomy tubes can be inserted. For infants and young children who continue to have recurrent episodes of acute OM despite tympanostomy tubes, manifested by otorrhea, a daily prophylactic dose of an antimicrobial agent is usually effective.

In a study by Mandel et al[22] of 109 children who had chronic middle ear effusion unresponsive to antimicrobial therapy, myringotomy and tympanostomy tube insertion resulted in less OM and better hearing than myringotomy alone or no surgery. However, the tubes did cause otorrhea, and persistent perforation occurred in a few patients. The subjects in this study were followed up for 3 years, during which time 50% of subjects underwent one myringotomy and tympanostomy tube procedure. A second procedure was required in an additional 30%, and a third procedure in the remaining 20%. Myringotomy provided no advantage over no surgery; both options had a high incidence of treatment failures. Figure 1 shows the efficacy of myringotomy and tympanostomy tube insertion over myringotomy alone or no surgery.

Adenoidectomy with or without tonsillectomy for prevention of OM has been evaluated over the past 30 years,[28-31] but only during the last few years have

TABLE 2. EFFICACY OF VARIOUS TREATMENTS IN 578 CHILDREN WITH CHRONIC OTITIS MEDIA WITH EFFUSION

Outcome During 2-Year Follow-up	*Myringotomy*	*Myringotomy and Tube Insertion*	*Adenoidectomy and Myringotomy*	*Adenoidectomy, Myringotomy, and Tube Insertion*
Time with effusion (%)	49.1	34.9	30.2	25.8
Time with hearing loss ≥20 dB (%)	37.5	30.4	22.0	22.4
Median time to first recurrence (d)	54	222	92	240
Surgical retreatments (No.)	66	36	17	17

Modified from Gates et al.[24]

TABLE 3. EFFICACY OF ADENOIDECTOMY FOR RECURRENT OTITIS MEDIA IN CHILDREN PREVIOUSLY TREATED WITH TYMPANOSTOMY TUBE PLACEMENT

Follow-up Year	*Treatment Group*	*No. of Subjects*	*Mean No. of Otitis Media Episodes*	*p**	*Proportion of Days Otitis Media Present*	*p**
First	Adenoidectomy	48	1.06	.51	15.0	.04
	Control	38	1.45		28.5	
Second	Adenoidectomy	45	1.09	.01	17.8	.005
	Control	27	1.67		28.4	

Modified from Paradise et al.[25]

*χ^2 test.

there been well-controlled randomized clinical trials. In one, Maw[23] studied 103 children from Bristol, England, all of whom had chronic middle ear effusion; unfortunately, the subjects were not given antimicrobial treatment prior to random assignment. Maw showed that adenoidectomy was more effective than no surgery, and that tonsillectomy did not add substantially to the efficacy of adenoidectomy alone (Fig 2[23]).

A subsequent study by Gates et al[24] of 578 4- to 8-year-old Texas children, all with chronic middle ear effusion unresponsive to antimicrobial therapy, showed that adenoidectomy and myringotomy with or without tympanostomy tube insertion was more effective than myringotomy alone with or without tube insertion. As in the Mandel study, myringotomy had the poorest outcome of the various surgical options (Table 2[24]). Gates et al concluded that adenoidectomy and myringotomy should be recommended over adenoidectomy and myringotomy with tube insertion because of the high incidence of otorrhea in children with tubes. However, when OM recurred after adenoidectomy and myringotomy, it occurred earlier when tube insertion had not been performed.

More recently, Paradise et al[25] conducted a randomized clinical trial of 99 children with previous tympanostomy tube insertion and recurrence of OM after spontaneous tube extrusion. For these at-risk children, adenoidectomy was effective over a 2-year period. The effect was greater for middle ear effusion than for recurrent acute OM (Table 3[25]).

Although recent randomized clinical trials provide a great deal of information regarding surgical indications for OM, it must be remembered that these trials had specific entry criteria and many patients were excluded. In everyday practice, decisions for or against surgical intervention should be individualized. Decision-making should include a number of considerations: 1) frequency, duration, and severity of OM (including degree of hearing loss); 2) whether appropriate and adequate medical management was provided; 3) patient age, since adenoidectomy and tonsillectomy present a somewhat greater risk in infants; 4) anesthetic risk, since most physicians would not recommend surgery on the pharynx in such cases, unless respiratory tract obstruction is severe; 5) time of year, since in the summer an older child may want to swim and tympanostomy tubes would be less desirable; 6) other indications for surgery on the ears or pharynx, such as deformity of the eardrum (eg, a deep retraction pocket) or sleep apnea due to obstructive tonsils or adenoids, making the decision for surgery more compelling; and 7) whether a patient is from a population known for a high incidence of chronic ear disease (eg, cleft palate or Down's syndrome) and may benefit more from timely tympanostomy tube insertion than from a wait-and-see attitude.

CONCLUSION

Despite a lack of complete information, the physician has enough evidence available to decide who is most likely to benefit from tonsillectomy and adenoidectomy. Indications are that tonsillectomy can benefit some children with frequently recurring throat infection and that adenoidectomy can reduce morbidity from OM.

Other trials yet to be conducted, concluded, or reported may yield answers to still-remaining questions. There is a need to improve the selection process for surgery when prevention of recurrent throat infection or OM is a goal. The effectiveness of tonsillectomy in the presence of upper airway obstruction should be tested in controlled, randomized trials. Tonsillectomy and adenoidectomy are known to be beneficial when sleep apnea and cor pulmonale are complications of upper airway obstruction, but indications for surgery in less severely affected infants and children are less distinct. In addition, randomized trials are needed to test the effectiveness of antimicrobial therapy as an alternative to surgical intervention for recurrent or chronic upper respiratory tract obstruction due to infected tonsils and adenoids. Information from future trials should improve the decision-making process and in turn enhance the quality of health care for patients who suffer from recurrent or chronic throat infection, upper airway obstruction, and OM.

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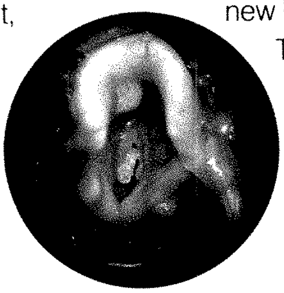
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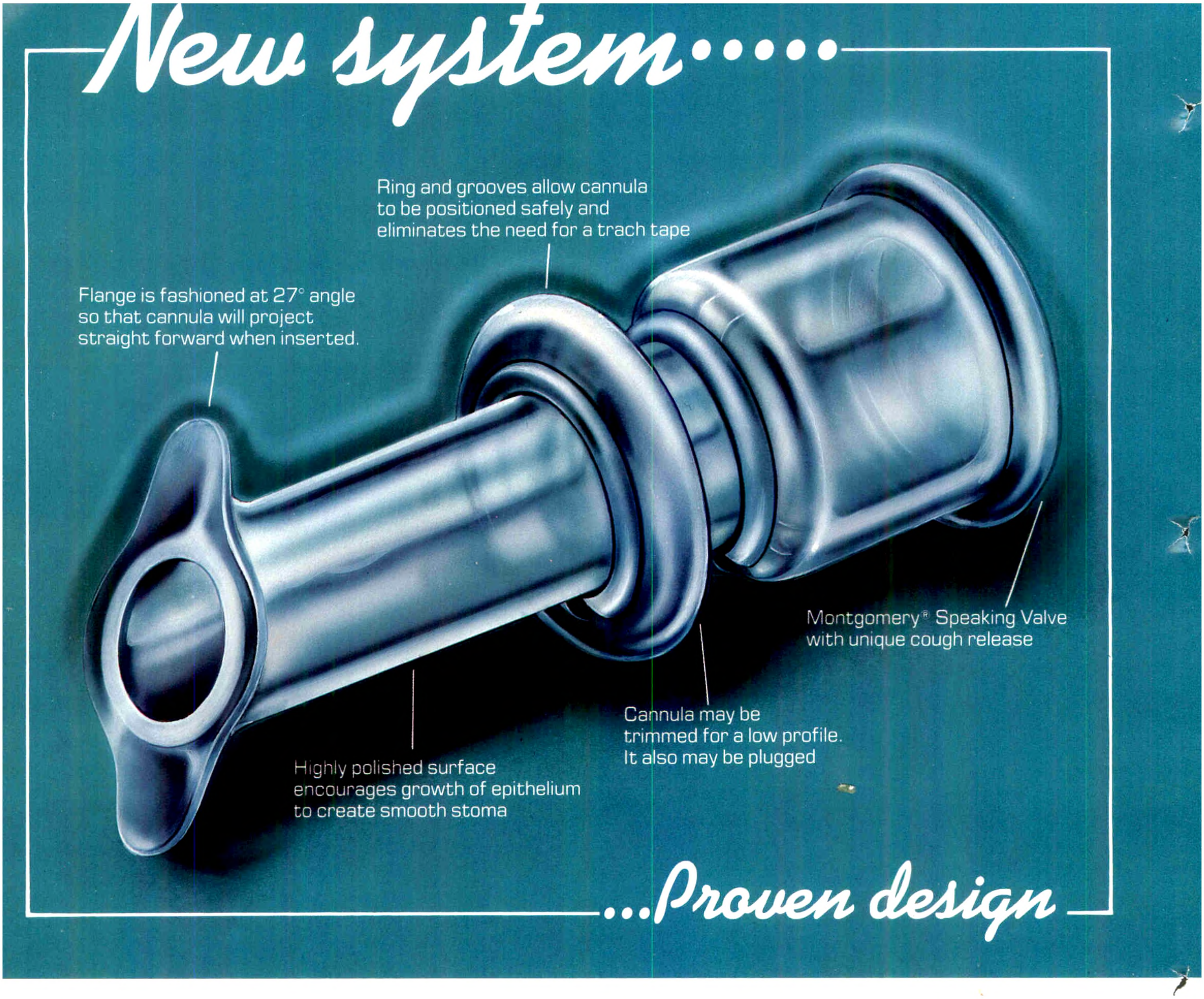
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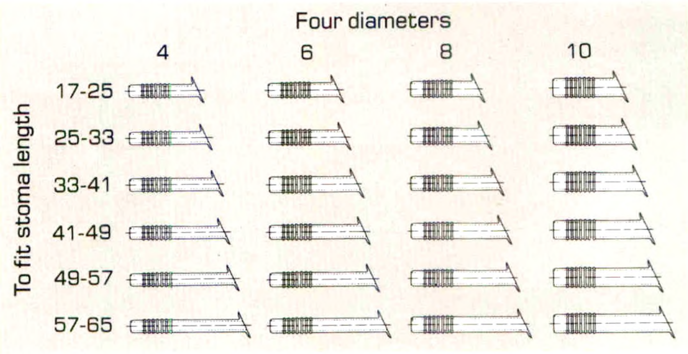

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EDITORIAL

THE FUTURE: WHAT DOES IT HOLD?

At this moment when the *ANNALS* celebrates its 100th anniversary, it is tempting to look internally and point to the accomplishments of past editors and the present growing internationalization of the *ANNALS*. It is a point of interest to note that the majority of papers in the December issue were from overseas, and stood the same scrutiny of peer review as domestic articles. Authors in other countries are increasingly seeking a greater readership of their work in one of the world's three premier otolaryngology journals, all of which are in America. Each has five to six times the subscribership of their own national journals.

However, the fascination is greater to look outward, to our whole specialty, and to how it has so tumultuously changed in the past 30 years.

When I was a resident in the 1950s my teacher-heroes were Albert Furstenberg, Howard and Bill House, Jerry Hilger, James Maxwell, and others, most of whom would do a mastoidectomy and submucous resection and hemilaryngectomy all in the same morning and not consider it unusual. This otolaryngic universality is still common in private practice but has virtually disappeared in academic practice. At all levels of academics today, from professor to assistant professor, all have subspecialized. It seems clear this is the pattern of the future. In the Iowa training program graduating residents started opting for fellowships in 1982, and at this time 10 years later, 80% subspecialization is the rule. This pattern does not at all mean that residents going into private practice will not perform what they were trained in and do it well. Indeed, they do, from my vantage point in a midwest tertiary care center.

Otolaryngology in the United States since its inception about 110 years ago has undergone three great eras and is now commencing its fourth. The first was in the early 1920s when a growing number of surgeon-physicians in this country went to Europe for a year of experience and training in ophthalmic and otologic surgery. The most frequented place was Vienna, Austria. When they returned they announced their practices were limited to those spheres, and thus the first medical specialty in this country was born. To be referred to "a specialist" at that time was to be sent to an EENT man. There were no other clinical specialties and no examining and certifying boards. The first board was Ophthalmology, and the second Otolaryngology a few years later, in 1926.

The second era began slowly in the 1930s when academic departments of EENT began to split into Ophthalmology and Otolaryngology, beginning as far as I can tell at the University of Michigan and rapidly replicated across the country.

Following this, in the 1940s the third era commenced with the emergence of the giants of American otolaryngology who made this country the font of the specialty beginning, I believe, with Dr Harris P. Mosher of Harvard. Some greats, the names of whom all young otolaryngologists today must honor are Mosher, Lierle, Furstenberg, Meltzer, Boies, Hilger, House, and Lempert, to name but a few. It was also in this era when there occurred two other major changes in the specialty. The first was the adoption of surgical authority in the whole head and neck (with the exception of the eyeball and brain), leading to the inclusive new name of our specialty. The second was the development of basic research laboratories throughout many of our departments and sections made possible by funds from the National Institutes of Health, enabling us to attract talented PhDs to apply their skills to our special problems such as deafness and cancer, and to train MDs in basic research.

The fourth era of our specialty is that which we are just now entering. It is the age of wide subspecialization. This has developed because so many otolaryngologists have decided they simply cannot master all the intricacies of our whole specialty and have confined their practices to one or more of its divisions. These are a) General Otolaryngology including basic otology, basic head and neck and cosmetic surgery, and rhinosinusology, b) Otology, Neurotology and Skull Base Surgery, c) Head and Neck Plastic and Reconstructive Surgery, d) Head and Neck Oncologic Surgery, and e) Pediatric Otolaryngology, the newest. Most of us will practice some mix of all these divisions of our specialty, but it is recognized universally that each is a firmly established discipline in our field. We wish to each of these divisions health, vigor, and prosperous research in this new era.

The future does, indeed, look bright.

* * *

As a special feature of this anniversary the journal will print in most issues an "*ANNALS CLASSIC*" culled from one of our 100 past volumes, which is of historical and also clinical interest. The first is in this issue, written by Albert C. Furstenberg, MD, and colleagues, entitled "Ménière's Symptom Complex: Medical Treatment." It is a model to be emulated by young writers. Also notable is that it is the first presentation of the medical regimen, ie, a diuretic and low salt diet, which is the backbone of our treatment to this day — and it was written over a half century ago!

Brian F. McCabe, MD
Editor

ANNALS MEMORABILIA
1892-1991

INTRODUCTION

Commencing with this issue, the *ANNALS* celebrates 100 years of publication. We have reproduced in these pages our Prospectus, drafted by the journal's founder, Dr James Pleasant Parker, and published with the first issue in January 1892. The *ANNALS OF OPHTHALMOLOGY AND OTOLOGY* was targeted originally at "busy progressive practitioners of medicine in the Western and Southern States," general physician and specialist alike. It was located in Kansas City, Missouri, and published quarterly, with a subscription price of $2.00 per year. Dr Parker projected originally that each issue would contain 80 pages of material. As revealed in the first Table of Contents, the first issue was heavily devoted to ophthalmology. But journal space became increasingly precious as manuscript submissions from otology, laryngology, and rhinology grew rapidly in number. The size and scope of the journal became unwieldy. (Its explosive growth is well documented by our fourth Editor, Dr Arthur Proetz, in his 1941 essay in honor of our golden anniversary, also reproduced here.) By as early as 1897, ophthalmology had disappeared from the journal's pages, and our current title, *ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY,* had been adopted, and the direction of the journal had been set.

Only six individuals have held the office of the Editor of the *ANNALS* during the past 100 years — a testament to the journal's stability and enduring standards of consistency and quality. The ownership of the journal continues with descendants of Dr Hanau W. Loeb, its second Editor: Mary G., William S., and Kenneth A. Cooper, Jr, of St Louis. It has been held by this family since 1924.

Editorially, the journal is under the direction of Dr Brian F. McCabe, Professor and Head, Department of Otolaryngology–Head & Neck Surgery, University Hospitals and Clinics, Iowa City, Iowa. Dr McCabe assumed the Editorship in 1982 and continues to oversee the peer-review process and to determine editorial policy. Dr McCabe personally approves the contents of every issue, as has each Editor before him. The journal has expanded to accommodate three Associate Editors, currently Dr Charles D. Bluestone, Pittsburgh, Pennsylvania; Dr Lee A. Harker, Omaha, Nebraska; and Dr. Lawrence W. DeSanto, Scottsdale, Arizona. Other important features in the journal are handled by Dr Kenneth A. Dolan (Imaging Case Studies), Dr John G. Batsakis (Pathology Consultations), Dr Dennis A. Pappas (Book Reviews), and Dr Kevin T. Kavanagh (Computer Applications).

Throughout 1992, the journal will feature carefully selected reproductions of landmark articles that have appeared over the past 100 years, under the heading "*ANNALS CLASSIC.*"

In his brief Editorial of January 1982, Dr Ben H. Senturia, our fifth Editor, summarized what he and the Cooper family considered to be the *ANNALS'* prime objective for the future: "to produce one of the finest possible ear, nose and throat journals in the world." This echoes the sentiments expressed by Dr Parker in his Editorial of 1893, and indeed our own outlook for our next century: "In the same spirit we now send forth the *ANNALS* to its thousands of readers, confident that future years will justify the resolve to make our periodical a worthy exponent of American medicine in its chosen special fields."

Michol L. Sheridan
Managing Editor

VOL. I. JANUARY, 1892. NO. 1.

ANNALS
OF
OPHTHALMOLOGY
AND
OTOLOGY.

A JOURNAL OF PRACTICAL OPHTHALMOLOGY, OTOLOGY, LARYNGOLOGY, AND RHINOLOGY.

EDITED BY

JAMES P. PARKER, M.D.

Published Quarterly.

KANSAS CITY, MISSOURI:
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PROSPECTUS

OF THE

ANNALS OF OPHTHALMOLOGY AND OTOLOGY.

1892.

IT is believed by the Incorporators of the Association under the authority of which the ANNALS OF OPHTHALMOLOGY AND OTOLOGY is published, that with the recent great advances made in medical science and art, the time has come when the busy progressive practitioners of medicine in the Western and Southern States will give substantial support to a Periodical devoted to PRACTICAL OPHTHALMOLOGY AND OTOLOGY, including their allies, RHINOLOGY AND LARYNGOLOGY.

The Annals is published with the following aims:

1. To afford Specialists, with well-earned reputations, a medium for communicating the results of their observation and research, and to disseminate meritorious contributions to the literature of OPHTHALMOLOGY, OTOLOGY, RHINOLOGY, AND LARYNGOLOGY, giving especial attention to PRACTICAL ARTICLES devoted to Medical Ophthalmology, Ophthalmoscopy, and the Pathological relations between the Eye, Ear, Nose, or Throat, and the general system. It is hoped that the interests of the General Surgeon and Physician, as well as of the Specialist, will alike be subserved by such a Journal.

2. To furnish a brief condensed REPORT OF PROGRESS in the four important departments of Medical Science mentioned, in which shall be recorded the most recent advances of real and permanent value and practical interest, from the current medical literature of the World. These reports will be written by specialists well qualified for the work.

Each number of the ANNALS will contain about eighty pages, and will be issued quarterly. The yearly volume will thus contain about three hundred and twenty pages, fully indexed.

The subscription price will be Two Dollars per annum, in advance.

Address all communications to the editor,

JAMES P. PARKER, M.D.,
S. E. Cor. 12th St. & Grand Ave.,
KANSAS CITY, MO.

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CONTRIBUTORS TO VOLUME I.

BELL, JAMES H., M. D., of Philadelphia.
BERENS, T. PASSMORE, M. D., of New York.
BUMSTEAD, S. J., M. D., of Decatur, Ill.
BURNETT, CHARLES H., M. D., of Philadelphia.
BURNETT, SWAN M., M. D., Ph. D., of Washington, D. C.
CHISOLM, JULIAN J., M. D., LL. D., of Baltimore, M. D.
CLAIBORNE, JOHN HERBERT, M. D., of New York.
DAYTON, W. L., M. D., of Lincoln, Neb.
DeSCHWEINITZ, G. E., M. D., of Philadelphia.
EATON, F. B., M. D., of Portland, Oregon.
FOX, L. WEBSTER, M. D., of Philadelphia.
FRYER, B. E., M. D., of Kansas City, Mo.
GLEITSMANN, J. W., M. D., of New York.
GOULD, GEORGE M., M. D., of Philadelphia.
HAMMOND, L. J., M. D., of Philadelphia.
HANSELL, H. F., M. D., of Philadelphia.
HARDIE, T. MELVILLE, B. A., M. D., of Chicago.
HARRIS, THOMAS J., M. D., of New York.
JACKSON, EDWARD, M. D., of Philadelphia.
KEYSER, PETER D., M. D., of Philadelphia.
LEDERMAN, M. D., M. D., of New York.
MAGEE, R. S., M. D., of Topeka, Kas.
MALONEY, J. A., M. D., of Washington, D. C.
MARBOURG, E. M., M. D., of Pueblo, Colo.
MICHEL, MIDDLETON, M. D., of Charleston, S. C.
MINOR, JAMES L., M. D., of Memphis, Tenn.
MULHALL, J. C., M. D., of St. Louis.
OLIVER, CHARLES A., M. D., of Philadelphia.
PATTERSON, E. B., M. D., of Michagamme, Mich.
PERCIVAL, ARCHIBALD, M. A., M. B., B. S., Camb., of Newcastle-on-Tyne, England.
POMEROY, OREN D., M. D., of New York.
PORTER, WILLIAM, M. D., of St. Louis.
RISLEY, SAMUEL D., M. D., of Philadelphia.
ROOSA, D. B. St.JOHN, M. D., LL. D., of New York.
SEILER, CARL, M. D., of Philadelphia.
SMITH, S. MacCUEN, M. D., of Philadelphia.
SPALDING, J. A., M. D., of Portland, Maine.
STEVENS, GEORGE T., M. D., of New York.
STEWART, JOHN S., M. D., of Philadelphia.
TURNBULL, LAURENCE, M. D., Ph.G., of Philadelphia.
WALLACE, JAMES, M. D., of Philadelphia.
WOLFNER, HENRY L., M. D., of St. Louis.
WOOD, CASEY A., C. M., M. D., of Chicago.
WÜRDEMANN, H. V., M. D., of Milwaukee, Wis.

TO CONTRIBUTORS.

Communications are invited from all parts of the world.

Authors who purpose favoring the ANNALS OF OPHTHALMOLOGY AND OTOLOGY with contributions are requested to observe the following:—

1. In accepting an article for publication under the head of "ORIGINAL COMMUNICATIONS" it is done with the understanding that it is to be contributed to the ANNALS *exclusively*, and that copies or abstracts of the same have *not* been and will *not* be published in any other journal.

2. Writing must be distinct and plain, and *especially all proper names.* (If possible a manuscript should be typewritten.)

It might appear presumptuous on the part of the youthful editor-in-chief to attempt to revise the work of his seniors, therefore all papers will be printed as written.

3. Proofs will be furnished authors for correction and revision, but it is requested that alterations be limited to what is of essential importance, as changes in the copy are equivalent to resetting and cause additional expense and much annoyance.

Authors should return corrected proof-sheets promptly.

4. The ANNALS especially desires brief, mature, concise articles on practical subjects, as its readers are busy practitioners who desire results, therefore the author who condenses expression enhances the value of his contribution and is rewarded by having it extensively read.

5. Authors will recieve gratuitously twenty-five reprints of their articles, in pamphlet form, with good covers, handsomely printed on the finest quality of book paper. If a greater number is desired they will be furnished at cost of press work, paper and binding.

The ANNALS is published four times a year: JANUARY, APRIL, JULY and OCTOBER, and all original articles should be ready to place in the hands of the printer sixty days before date of publication.

Address all communications to

DR. JAMES P. PARKER,
S. E. Cor. Garrison and Lucus avenues,
St. Louis, Mo.

A WORD TO THE READERS OF THE ANNALS.

We are not a little proud to congratulate both ourselves and our readers that the ANNALS OF OPHTHALMOLOGY AND OTOLOGY can no longer be considered an experiment.

To ourselves, indeed, there never was any doubt about it, but in the present undue multiplication of medical journals it may have seemed to some as one of the many ventures destined to be ephemeral.

So great has been the sympathy of the profession, and so tangible its evidences, that we can confidently base the conviction of the permanency of the ANNALS upon the present subscription list, even if this list did not show an uninterrupted daily growth.

From all over our own country and from English-speaking peoples everywhere, there has been a steadily increasing offer of words of praise, of scientific contributions, and of subscriptions.

Our readers know by experience that they have been little worried by the verbose and useless inflictions of editorial vanity and appeal. Instead of this we have trusted in the strength of facts, believing that to "do the deed and say naught about it" is the proper way to gain the confidence of discerning medical men.

From the first we have relied upon no adventitious aids or outside business, to establish and maintain our position, but we have resolutely held fast to purely professional and scientific ideals and interests.

In the same spirit we now send forth the ANNALS to its thousands of readers, confident that future years will justify the resolve to make our periodical a worthy exponent of American medicine in its chosen special fields.

THE ANNALS: 1892-1941

ARTHUR PROETZ, M.D.

ST. LOUIS

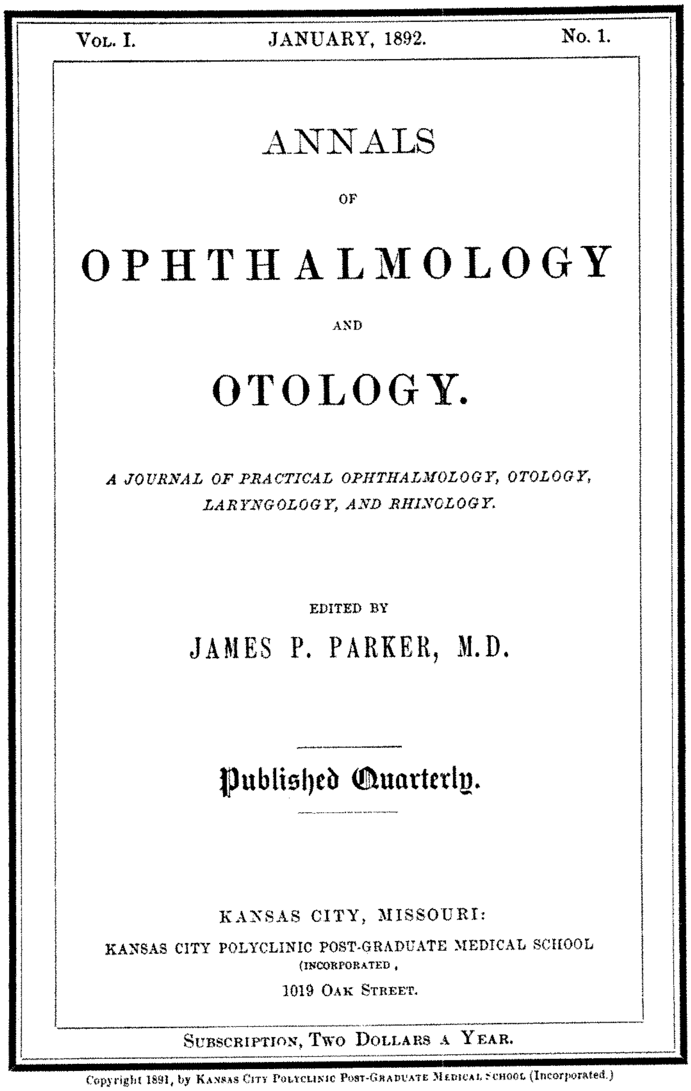
The history of the ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY is the history of otolaryngology reflected in a peculiarly relevant manner. From the beginning its articles appear to have been selected with conservatism and judgment, and there is little to be found in its pages that has to do with the visionary and the transient.

This Journal first saw the light in January of 1892, and the place of its nativity is Kansas City. It first appeared as the Annals of Ophthalmology and Otology under the editorship of James Pleasant Parker, M.D., who received all communications and "$2.00 per annum in advance," at the southeast corner of Twelfth Street and Grand Avenue.

According to the prospectus it was believed that "the time has come when the busy, progressive practitioners of medicine in the Western and Southern states will give substantial support to a Periodical devoted to Practical Ophthalmology and Otology, including their allies, Rhinology and Laryngology." In those days ophthalmology and otology flourished together, while rhinology and laryngology were often linked with diseases of the chest. It was not many years before the reputation of this modest Journal spread from the "Western and Southern states" to the wide world, which has continued to give it the hoped for "substantial support."

The first issue comprised 74 pages. The initial Board of Editors headed by Doctor Parker, then Secretary of the Kansas City Polyclinic Post-Graduate Medical School, consisted of Doctor B. E. Fryer of Kansas City, Doctor Casey A. Wood and Doctor T. Melville Hardie of Chicago, and Doctor M. D. Lederman of New York City. The first editorial page announced that "original contributions are invited from all parts of the world. Those accepted, upon publication, will be liberally paid for. *It is to be understood that such articles are contributed exclusively to this Journal.*"

The first article was by D. B. St. John Roosa, M.D., LL.D., Professor of Diseases of the Eye and Ear, New York Post-Graduate



VOL. I. JANUARY, 1892. No. 1.

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Medical School and Hospital—Surgeon to the Manhattan Eye and Ear Hospital, and was entitled "The Best Operation for the Extraction of Cataract."

There were in this first number five articles directed to otolaryngologists:

"Excision of the Membrana Tympani and Necrotic Malleus in Four Cases of Chronic Suppurative Otitis Media." By Charles H. Burnett, A.M. M.D. of Philadelphia.

"Deafness the Result of the Poison of Syphilis; Its Treatment by Muriate of Pilocarpine in Acute Syphilitic and Labyrinthine Disease of the Internal Ear; Also Its Use in Chronic Disease of the Ear with Labyrinthine Symptoms." By Lawrence Turnbull, M.D. Ph. G. of Philadelphia.

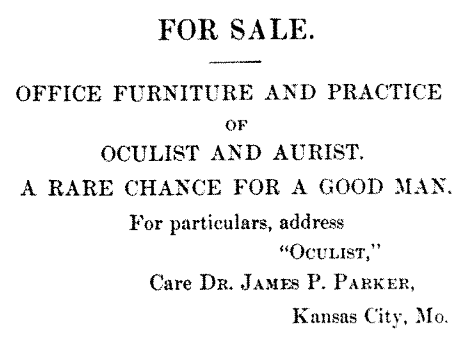
"Otacoustic Treatment in Chronic Deafness." By J. A. Maloney, M.D. of Washington, D. C.

"Traumatic Hemorrhage of the Tympanum Causing Deafness with Subsequent Restoration of Hearing with Report of Cases." By S. MacCuen Smith, M.D. of Philadelphia.

"The New and Simple Method to Lessen Reaction After the Use of the Galvano-Cautery for Nasal Hypertrophies." By J. W. Gleitsmann, M.D. of New York.

At the very beginning the tail appears to have begun wagging the dog. Pages 210 and 211 tell the story. On the one is printed "*Special Notice—Removal. The* ANNALS OF OPHTHALMOLOGY AND OTOLOGY *has been REMOVED* from Kansas City to *ST. LOUIS, MO. . . . Assurance is given that the ANNALS will continually be chosen by the leading Specialists on both sides of the Atlantic for the presentation of meritorious contributions.*" Already the "Western and Southern states" were giving way to "both sides of the Atlantic," and the price mounted to $3.00. We read no more offers to pay liberally for accepted material.

The notice on the opposite page completes the picture:



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At the end of the first year Parker wrote editorially "We are not a little proud to congratulate both ourselves and the readers that the Annals of Ophthalmology and Otology can no longer be considered an experiment. . . . Our readers know by experience that they have been little worried by the verbose and useless inflictions of editorial vanity and appeal. Instead of this we have trusted in the strength of facts, believing that to 'do the deed and say naught of it' is the proper way to gain the confidence of discerning medical men.

"From the first we have relied upon no adventitious aids or outside business to establish and maintain our position, but we have resolutely held fast to purely professional and scientific ideals and interests."

But now things began to get really out of hand. The first volume had 212 pages, the second doubled this as Parker moved to St. Louis. By Volume 4 there were some 640 pages. Defensively Parker wrote, "The number of good original papers offered to the Annals continues to increase. . . . When two or more original articles upon the same subject are received, the shortest, most pithy and concise will take precedence." But it was no good. Volume 5 (1896) showed up with 1380 pages. The publication was now split into four journals: The Annals of Ophthalmology, The Annals of Otology, The Annals of Neurology and the Annals of Rhinology and Laryngology. The whole was under the management of a staff of ten and the rhinology and laryngology fell to H. W. Loeb.

1897 brought Volume 6, reduced once more to portability and bearing its present title, THE ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY. It was now published by a brother of the founder and edited by a board of seven.

Among the contributors to Volume 1 we find Edward Jackson, then of Philadelphia, and Thomas J. Harris of New York, both still active in their specialties, still to be seen at meetings and both still taking a prominent part in the direction of educational thought.

In Volume 6 (1897), the first under the new name, appear Thomas Hubbard and J. F. Barnhill. Hubbard wrote on a topic not entirely ignored by present writers: "Angio-Neurotic Edema and Certain Vaso-Motor and Trophic Disturbances of the Mucous Membrane of the Respiratory Tract." In this volume there were only 25 original communications and hundreds of abstracts from the literature. Of the 25 original communications, 10 were case reports and descriptions of new instruments. There appeared also the Proceedings of the American Laryngological Association at

Washington, May 4, 5 and 6, 1897, the Proceedings of the American Laryngological, Rhinological and Otological Society, held in the same city, and the Proceedings of the French Otological Society, reported by J. Holinger, M.D. of Chicago.

At the close of the century the subject matter under discussion differed not very materially from that which occupies the journals of the present time, with a few notable exceptions. One of these was diphtheria. The index to Volume 7 devotes a special section comprising 34 titles to the disease. In this volume there are also four accounts of foreign bodies impacted in the esophagus, three of them requiring esophagotomy for their removal. There is described an instrument consisting of "a twisted stem or rod joined to a flattened handle together about 15 inches long. One end of the rod is bifurcated three inches, forming a closed loop. This loop is bent upon itself into two parallel loops an inch long and about half an inch apart, the part joining the parallel loops forming the beak of the instrument, which is placed at an angle of 45 degrees to the plane of the posterior parts of the loops and one-quarter of an inch from this plane.

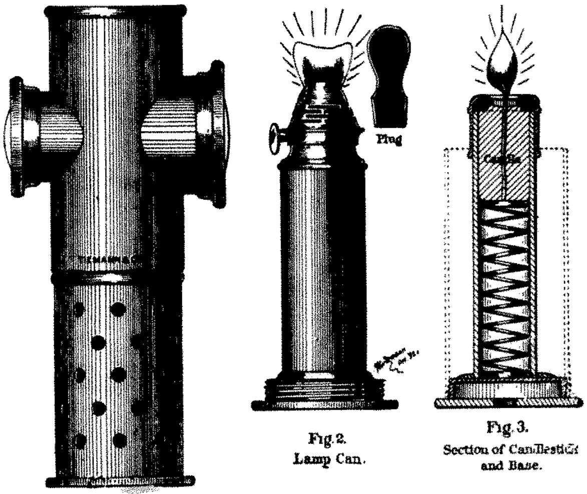

Fig. 1

Fig. 2.
Lamp Can.

Fig. 3.
Section of Candlestick and Base.

The first illustration, from Volume I. A portable bedside lamp.

"The coin or similar shaped foreign body is caught by the beak, deflecting into the parallel loops, and upon withdrawing the instrument the coin is drawn up with it".

In 1900 there was an article on the use of the new suprarenal extract in the nose. Its preparation, chemical and physiological properties were described and it was concluded that "the suprarenal extract is a powerful astringent without objectionable properties".

A case of acute thyroiditis of rheumatic origin was described.

The war between the external and internal sinus operators had already begun. Many an instrument was presented for the sewing, crushing and splinting of deflected septa and Doctor J. L. Goodale submitted some of the now endemic before-and-after photographs of patients with nasal deformities, but the most arresting title is undoubtedly "The Surgical Treatment of Otic Sclerosis by Doctor Ricardo Botey of Barcelona, translated by Albert Miller of St. Louis". The approach was endaural and the decompression consisted in the "mobilization of the stirrup after cutting adhesions to the border of the fenestra ovalis". Sometimes the stirrup was removed. Specimens and animal experiments were described. There are ten conclusions, the final one: "Since it is almost certain that otic sclerosis is a tropho-neurosis, with formation of connective and osseous tissue, principally in the labyrinthine capsule, round about the fenestra ovalis, in the cochlear canal and even in the helices of the cochlea, the neuro-epithelial terminations of the auditory nerve being more or less involved, surgical treatment of sclerosis of the ear is in nearly all cases useless".

1900 marked the accession to the editorship of Hanau W. Loeb of St. Louis, who was to retain the position until 1928 and to whom the ownership of the ANNALS finally passed. Through his guidance the Journal enjoyed a vigorous youth and a robust adolescence and his name became inseparably linked with it, so that it was known to most of his friends as 'Loeb's Journal'.

To those who knew Doctor Loeb it was patent that the quality of the early volumes would be maintained or improved. He was always very jealous of the standing of his publication and chose his material with great care.

While there is little in the early volumes which might be considered obsolete at this time, there is a notable absence of certain topics with which we are now familiar. Radiology is rarely mentioned and then only in connection with foreign bodies. There was no arsphenamine, no lipiodol and no vitamin. Allergy was met with only in its earlier guises of vasomotor rhinitis and asthma.

Some famous names appear: Jonathan Wright on Empyema of the Sphenoid Sinus with Delirium, Johann Sendziak on Laryngeal

Disturbances in Tabes, Samuel Allen on Lupus, LaFayette Page on Disease of the Upper Air Passage Relative to Mental Development, Alexander Randall on the Recording of Ear Cases, Joseph Beck on Pharyngeal Hyperkeratosis and George W. Crile on Operations for Malignant Disease.

Number 4 of Volume 11 (1902) contains the papers of the Sections of Laryngology and Otology of the British Medical Association with Gruenwald, Lack, Dundas Grant, Rohrer and Watson among the contributors.

In 1902 a few half-tones began to appear of a quality not above criticism, but in the following year small sections of the book were printed on glazed paper and the illustrations improved. In those days, as today, it was the particular concern of the publisher to select long-lived paper for his journal and even the early numbers are still free from discoloration.

While in the early volumes there are copious references to the transactions of the major special societies here and abroad there is none to an American otolaryngological journal prior to the Laryngoscope, which appeared in 1896. Presumably therefore the ANNALS was the first otolaryngological journal in America.

Under Loeb's aegis the ANNALS flourished and made many friends. Considerable numbers of its present subscribers have been on the rolls since the early days.

In 1927 Doctor Loeb died. The distinguished contributors to the Memorial Issue published in his honor the following year testify to the high regard which he and his journal enjoyed.

With a deep sense of obligation both to Doctor Loeb and to American laryngology, the editorship was assumed by L. W. Dean and Arthur Proetz, although the ownership of the Journal continued in Doctor Loeb's family where it remains today.

To mark the fiftieth year in the life of the ANNALS and to express in a fitting and concrete manner their acknowledgment of the debt which it owes to its many friends and contributors, the present editors have prepared this Jubilee Volume. The cordial response with which their invitation to participate in it has been greeted by the distinguished otolaryngologists of the country justifies the high hopes which the editors and managers hold for the future of the ANNALS.

A BRIEF HISTORY OF THE *ANNALS* 1892-1982

The year 1982 marks two important milestones in the history of the *Annals of Otology, Rhinology & Laryngology — Annals of Head and Neck Medicine and Surgery:* it is the 90th anniversary of our founding and the occasion of the appointment of our sixth editor, Dr. Brian F. McCabe.

The *Annals of Ophthalmology and Otology* was the title under which the journal was first published in Kansas City, Missouri, by Dr. James P. Parker in January 1892. The first volume consisted of 212 pages and was widely acclaimed. The reputation of the journal spread rapidly and by 1896 the number of published papers had increased so much that the fifth volume contained 1,380 pages. It was evident that the size of the journal had gotten out of hand, and in 1896 it was announced that the journal would be divided into the components of ophthalmology, neurology, otology, and rhinology and laryngology.

The publication devoted to the ear, nose and throat appeared in 1897 as Volume Six, under the title *Annals of Otology, Rhinology & Laryngology.* This volume contained 528 pages including 25 original communications, almost half of which are case reports or descriptions of new instruments. Abstracts constituted a large part of the earlier volumes, as did society proceedings of the American Laryngological Association; the American Laryngological, Rhinological and Otological Association; the French Otological Society and the Section of Laryngology and Otology of the British Medical Association. However, the balance shifted rapidly and original communications soon became the primary feature of the journal. In 1900, 34 papers were published along with the journal's first photomicrographs. Five years later the lead article was illustrated with the first color page which consisted of four drawings of mucous membranes and glands.

The name of Dr. Hanau W. Loeb appeared as a member of the Editorial Board from 1895 to 1899. In 1896 the demand for more rhinology and laryngology articles made it desirable to have a special editor in St. Louis, and Dr. Loeb assumed charge of these areas; later he purchased the journal and became its editor and publisher. A man of great intelligence and energy, Dr. Loeb helped organize the Marion Sims Medical College in St. Louis which later became the Medical Department of St. Louis University, was Head of its Department of Otolaryngology, and became Dean of the School of Medicine. He devoted great energy and fervor to improving the scientific standards of the journal and its reputation throughout the world. The *Annals* remained under Dr. Loeb's direction until 1926.

In 1927, Dr. L. W. Dean, Professor of Otolaryngology at Washington University School of Medicine, was appointed Editor-in-Chief; he immediately asked Dr. Arthur W. Proetz, one of his brilliant colleagues, to become his Associate Editor. After nine years of this arrangement, Dr. Dean named Dr. Proetz Coeditor and transferred to him major responsibility for the journal. Upon Dr. Dean's death in 1943, Dr. Proetz became Editor and continued in this capacity for 23 years.

Dr. Arthur Proetz was a brilliant scientist and an outstanding clinician and administrator; he was also a man of many interests and accomplishments which included photography, art, music and drama. It was no wonder that under his direction, the *Annals* grew progressively in scientific and editorial quality to become one of the outstanding otolaryngologic journals in the world.

It was my privilege to serve as Associate Editor under Dr. Proetz for eight years before assuming the editorship in 1966. As Clinical Professor of Otolaryngology at Washington University School of Medicine and Director of the Department of Otolaryngology at The Jewish Hospital of St. Louis, I was fortunate to know many authors whose research and clinical studies were important contributions to the *Annals.* During these past 15 years, the *Annals* has striven to maintain the highest standards, while aspiring at the same time to creative and thoughtful innovation. The changes to a bimonthly and to the larger journal format as well as the supplement program were enthusiastically received everywhere. In 1980, as part of a national trend to make journal titles reflect the more comprehensive nature of our specialty, the name of the journal was expanded to the *Annals of Otology, Rhinology & Laryngology — Annals of Head and Neck Medicine and Surgery.*

The *Annals* has become a fully international journal, with authors and subscribers in every part of the world. In terms of content, it clearly reflects the evolution and expansion which have characterized science, medicine and otolaryngology in this century. In 1981 the *Annals* published 143 papers and 11 supplements, and the journal is richly illustrated not only with color — 7 full pages — but also with a broad range of figures representing the most sophisticated technology of both medical science and the printer's art.

In 1982, on our 90th anniversary, we are very fortunate to have Dr. Brian F. McCabe, Head of the Department of Otolaryngology at the University of Iowa School of Medicine, assume the editorship of the *Annals.* Dr. McCabe is widely known for his many clinical, research and academic achievements. Under his direction, we look forward to progressive growth and the maintenance of continued high scientific and editorial standards.

Despite the inroads of inflation and high costs, the grandchildren and great-grandchildren of Dr. Loeb, who are the present publishers of the *Annals*, have informed Dr. McCabe that it is their desire that we continue to produce one of the finest possible ear, nose and throat journals in the world. It will be the prime objective of the editors and the editorial staff to fulfill this request.

Ben H. Senturia, MD

EDITORS OF THE *ANNALS*

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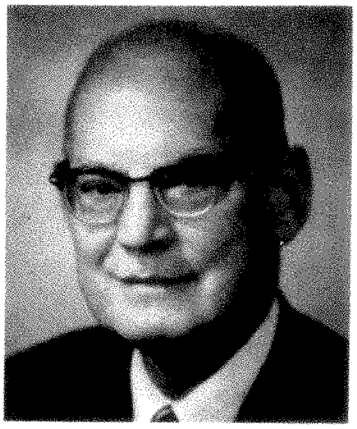
Founder, Editor and Publisher
1892-1896

HANAU W. LOEB, MD
Editor 1900-1926

L. W. DEAN, MD
Editor 1927-1935, Coeditor 1936-1943

ARTHUR W. PROETZ, MD
Associate Editor 1927-1935, Coeditor 1936-1943,
Editor 1944-1966



BEN H. SENTURIA, MD
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BRIAN F. MCCABE, MD
Associate Editor 1972-1975, Coeditor 1976-1981,
Editor 1982-

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MÉNIÈRE'S SYMPTOM COMPLEX: MEDICAL TREATMENT.*

A. C. FURSTENBERG, M. D.,

F. H. LASHMET, M. D.,

FRANK LATHROP.

ANN ARBOR.

Since the classical description of Ménière's disease was given to medical science in 1861, much speculation has occurred and many pertinent recommendations have been made, referable to the treatment of this symptom complex. For many years the therapeutic management of this malady has been a controversial matter and one in which a confusing number of remedies have been offered, based chiefly upon the hope that they might in some manner influence some of the many hypothetical, pathologic changes which are assumed to exist.

The sum total of these endeavors has been of little value to the patient and the causes of failure are clearly those of trial and error. Assuming, for example, that an increased secretion of cerebrospinal fluid is responsible for pressure upon the eighth nerve, the lumbar puncture is advocated. Or, considering the pathogenesis associated with the sympathetic and parasympathetic nervous systems, such drugs as pilocarpin, atropin and adrenalin are administered because of some pharmacologic action upon nervous tissue. Recent studies in the field of endocrinology which suggest a possible relationship between a glandular dysfunction and epilepsy, the latter seeming to be akin to Ménière's disease, have occasioned an investigation of the patient's calcium metabolism and prompted the use of thyroid, parathyroid and pituitary substances. Quinin, for its specific effect upon the auditory nerve, potassium iodid, for its empirical values, bacterins and vaccines for what they may be worth, and finally, the application of a seton to the nape of the neck, are the remaining therapeutic measures available for trial.

Theoretically, some appear to have merit. We do not doubt the value of lumbar puncture in certain cases of vertigo. The effect of free catharsis and pilocarpin sweats has properly given rise to much enthusiasm in others. These measures, conceived in good faith, have been promoted by an honest conviction that they have cured certain individuals of an intractable vertigo and that they are capable of doing the same for others. Yet who has not applied this large group of therapeutic possibilities only to end with a feeling of futility and a sense of despair. The lack of sustained practicability of medical therapy is constantly in evidence and, lest our claims appear presumptuous, may I add that the conclusions derived from our own studies are probably no exception to this fact.

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*Presented before the annual meeting of the American Otological Society, Atlantic City, June 7, 1934.

There are other obvious reasons for the bewildered and futile state of medical therapy in Ménière's symptom complex. Consider, for example, the enormous variety of vertigo syndromes to which medical treatment has been applied. The tendency to create a disease entity by grouping a number of cases having one symptom in common is one of the temptations of medical practice. Vertigo lends itself admirably to this evil. Every conceivable form of dizziness appears to have been classified as a disease and treated as such. Failure to designate disease entities properly and apply well directed treatment has made a correlation of results impossible. There exists, therefore, no uniformity of opinion in respect to the merits of the innumerable therapeutic measures which have been employed.

The point of the foregoing is that many otologists have made their own classification of Ménière's symptom complex. They have done so whimsically and without consideration of the scientific facts upon which a clinical entity is developed. It has been a term loosely applied and much abused. So much has this been true that many authors have urged the abandoning of the personal reference and the acceptance of a more precise nomenclature. No matter what justification may exist for such a change, it remains a fact, nevertheless, that the great French clinician described a syndrome definitely related to the acoustic nerve and one which has borne his name for nearly three-quarters of a century. I strongly suspect that future generations of our profession will continue to accord it this personal reference.

Consider the syndrome which is typically Ménière's symptom complex: It embodies well defined clinical manifestations which have been exhaustively treated in our medical literature and are well known to every student of otology. A simple glossary will suffice to enumerate and place on record the symptoms which characterized the disease as it was treated in the following studies: A violent attack of vertigo in a patient with deafness; occasionally impaired cochlear function on both sides, but more profound in the ear to which the symptoms are referred; nausea, vomiting and spontaneous nystagmus in the severe seizures; persistent tinnitus—often bilateral—increased during the paroxysm; vestibular tests of little significance—usually within the limits of normal; a pathetic picture of total disability in an individual suffering from a vertigenous attack, or living in the terror of an impending one.

The pathological changes responsible for the capricious symptoms of this syndrome still remain a mystery. They have been the subject of numerous studies, varying from conscientious research in the pathological physiology of the auditory mechanism to skillful adaptations of morbid processes to meet the clinical needs. They comprise voluminous works in our medical literature, quotations from which at this time would merely constitute a repetition of medical history. Suffice to say for those who hold that the pathological changes are in the internal ear, that statistical evidence indicates that the destruction of the otic labyrinth in a few cases has not been followed by relief of symptoms. To those who prefer the theory of morbid changes to the auditory nerve, I might add that microscopic examination of sections from the acoustic nerve in eleven cases failed to demonstrate pathologic alterations in the tissue submitted for study. In nine of the cases, relief immediately followed section of the nerve. In two of the cases the symptoms are still present after periods of two and four years. Dr. Konstantin Löwenberg, pathologist in our Psychopathic Department, in a recent study of autopsy material from a fatal case of tumor of the acoustic nerve, has made an extraordinary observation in the discovery of a normal nucleus in the presence of a completely degenerated auditory nerve. This amazing phenomenon, if sustained by further studies, would suggest an innervation of the nucleus from the opposite side and offer another site in the auditory system where the influences of pathologic changes might be felt. Obviously a nuclear lesion under such conditions would not be affected by section of the auditory nerve, and herein may lie a possible explanation for the failure, in rare instances, to obtain immediate and complete relief following severance of the acoustic nerve.

It is doubtful, therefore, if the clinical manifestations of Ménière's symptom complex can be definitely ascribed to any isolated part of the auditory tract. Rather is it more accurately assumed, perhaps, that any or all of its constituents may participate in the changes which give rise to a typical attack. There is some proof for this assumption in the observations already recorded, while the conclusions derived from our own studies do not tend to detract from this belief.

The theory which gave rise to the following investigation was first suggested to me by Dr. Samuel Kopetzky. To him, I gratefully accord full credit for the inspiration which led me into a most fascinating study. In September, 1933, he asked me the following questions: "What class of individuals have vertigo? Why are dizzy attacks frequently seen in patients with cardio-vascular-renal disease?" "The answer," he continued, "lies in some disturbance in the metabolism of water which gives rise, perhaps, to a water-logged condition of the static labyrinth. Why don't you study water balance in these patients?"

In acting upon Dr. Kopetzky's suggestion, I reviewed the medical literature for all available references on the subject. The only technical studies of interest were those of Dida Dederding of Copenhagen,[1] in 1929 and 1931, in which she advanced the idea that the symptoms in Ménière's disease were due to a disturbed metabolism of water.

She observed that patients were more likely to have an exacerbation of symptoms, when there was evidence of retention of body water. Furthermore, these patients were improved when they eliminated a large amount of water, as by profuse perspiration (pilocarpin) or polyuria (diuretics, chiefly salyrgan). She investigated this question by comparing the intake of fluid with the amount of urine excreted, and correlating the difference between them with changes in body weight. From the data so obtained she concluded that the symptoms of Ménière's disease were due to "an accumulation of water in the body," and that this fluid was probably "extra-cellular edema." From the data submitted there is no doubt that some justification for these conclusions exists, but there are certain aspects of this investigation which prevent complete acceptance of the explanation offered by Dederding.

First, edema, or the "accumulation of water in the body," is not water alone, but a solution of electrolytes, chiefly sodium salts, and water. Both of these substances, salts and water, are so dependent upon each other in maintaining isotonicity with the other body fluids that it is impossible to consider either alone. For example, when body water is lost by perspiration induced by pilocarpin, or by diuresis induced by salyrgan, a very definite amount of sodium salts is also lost in the process. One might ask then, if the relief of symptoms in Ménière's disease is not due more to the loss of sodium salts than to the water in which they are eliminated. Dederding does not consider this a possible explanation, although her data would support such a conclusion just as well as it does her assumption that water is specifically concerned.

Second, the method by which Dederding and her associates measured water exchange was so inaccurate that quantitative statements regarding the latter are impossible. If an accurate statement of water exchange is desired, the amount of water "into" the body from every "source" and the amount of water "out" of the body at every "exit" must be determined. As will be seen, only a small fraction of both the water "into" and "out" of the body was determined by Dederding.

Table 1 lists the various items of water "into" and "out" of the body and gives the average amounts of each as obtained under ordinary conditions with the normal subject. Examination of this table reveals several interesting facts.

TABLE I.—WATER EXCHANGE—BALANCE.

AVAILABLE WATER.	Grams.
1. Exogenous	
A. Diet	900
B. Water as such	1100
2. Endogenous	
A. Oxidation	200
B. Preformed	0
Total	2200

EXCRETED WATER.	Grams.
3. Urine	1000
4. Stool	200
5. Vapor	1000
Total	2200

The water contained in the solid food of the diet is a relatively large amount. The quantity of water derived from the oxidation of protein, fat and carbohydrates, although relatively small, is not slight enough to be neglected. The "preformed" water which is that water released from body tissue when the latter is destroyed, is absent when the subject is in energy balance, and therefore is of no significance here. Finally, the most interesting fact is that the "water as such," or the free fluid of the intake, constitutes less than 50 per cent of the total water available to the subject. Dederding determined only the free fluid intake in her investigations.

In considering the various losses of water from the body, a most surprising amount is lost by vaporization from the skin and lungs. This loss is comparable to the amount of water lost as urine and is rarely determined by those pretending to measure water exchange. The water contained in the stool is relatively small, but it is apparent that it, too, must be determined in an accurate water exchange. The water of the urine is the one loss most commonly determined, but it constitutes less than 50 per cent of the loss of water from the body. The quantity lost by vaporization is often greater, although it has seldom been considered in studies of water exchange. Dederding, in her investigations, determined only the urine volume.

It must be obvious that determination of the free fluid of the intake and the urine volume constitute less than 50 per cent of the total exchange of water by the body. Consideration of only these two items of water exchange often result in erroneous conclusions regarding the status of body water. The following examples (Tables 2 and 3) are given to demonstrate this fact. Table 2 shows the data obtained from a postoperative case of acute intestinal obstruction.

TABLE II.—WATER EXCHANGE—DEHYDRATION.

AVAILABLE WATER.	Grams.	EXCRETED WATER.	Grams.
1. Exogenous		3. Urine	700
A. Diet	0	4. Stool	750
B. Water as such	3000	5. Vapor	1000
2. Endogenous		6. Emesis	1500
A. Oxidation	225	7. Drainage	750
B. Preformed	200		
Total	3425	Total	4700

Daily dehydration 1275.

If one compared only the "water as such" (3,000 grams) with the urine water (700 grams), the daily dehydration of 1,275 grams would never have been suspected. Table 3 shows the data obtained from a subject having chronic nephritis and edema. If, in this subject one compared the "water as such" (1,200 grams, which is smaller than that of the subject in Table 2) with the urine water (800 grams, which is larger than that of the subject in Table 2), the daily accumulation of 550 grams of edema would have been overlooked.

TABLE III.—WATER EXCHANGE—HYDRATION.

AVAILABLE WATER.	Grams.	EXCRETED WATER.	Grams.
1. Exogenous		3. Urine	800
A. Diet	900	4. Stool	150
B. Water as such	1200	5. Vapor	850
2. Endogenous		Total	1800
A. Oxidation	250		
B. Preformed	0		
Total	2350		

Daily hydration 550.

The foregoing facts make it evident that investigations similar to those of Dederding are of value only when a method which insures a more accurate determination of water exchange is employed. The data presented below is the result of such an investigation.

Time does not permit a detailed account of the procedure by which an accurate statement of water exchange was obtained in this investigation. For these details, reference may be made to the original descriptive articles.[1] However, the following brief description is given in order to emphasize the care and precision which are imperative in such a study.

The subject was weighed in the nude state at definite intervals of either twelve or twenty-four hours on a special balance which is accurate to 1.0 gram. The drinking water ingested daily was accurately weighed in a large thermos bottle from which the patient drank through a glass tube. Throughout the experiment, the diet was constant, the same kinds and amounts of food being ingested day after day.* The food was prepared, accurately weighed and even served by one of us. The water content of the food was determined by dessication. The urine and stool were collected daily in closed pails, accurately weighed and the water content of each also determined by dessication. The daily excretion of nitrogen was obtained by Kjeldhal analysis of the urine and feces. The water lost by vaporization from the skin and lungs, and that available from the oxidation of the foodstuffs, was obtained by means of the insensible loss of weight and the metabolic mixture as described by Newburgh, Wiley and Lashmet.[2]

Thus, in this investigation, the water exchange was determined by quantitatively measuring every item of water "into" and "out of" the body.

The data presented in Fig. 1, was obtained from a patient who had had typical Ménière's disease for ten years. For about two years prior to this study he had averaged two or three attacks per week, and for the past six months had suffered a seizure daily. These attacks were characterized by a "feeling of fullness" in the head, "buzzing and ringing" in the ears, dizziness, and finally, nausea with vomiting. The only relief he had been able to obtain was secured by lying very quietly with eyes blindfolded.

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*The daily diet consisted of: Milk, 600 gms.; cream (40%), 100 gms.; cheese, 100 gms.; bread (whole wheat), 150 gms.; puffed wheat, 10 gms.; grape fruit (canned), 100 gms.; butter, 60 gms.; apple sauce, 150 gms.; sugar, 10 gms. Such a diet contained: Nitrogen 9.7 gms.; fat, 154 gms.; carbohydrate, 188 gms.; calories, 2382; total solids, 397 gms.; sodium, 87 milli-equivalents.

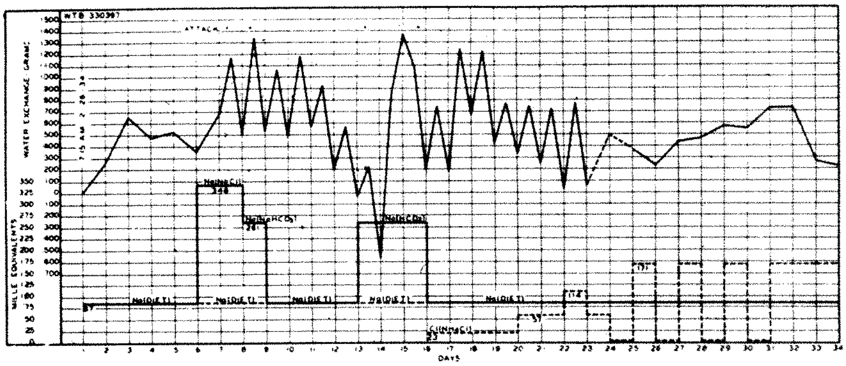

Fig. 1.

For the first six days of this investigation, water exchange was determined for periods of twenty-four hours. It was soon realized that changes in body water occurred so quickly that twelve-hour periods of determination were necessary. Consequently, for the remainder of the study, water exchange was measured for periods of twelve hours, one period beginning at 7:15 A. M. and ending at 7:15 P. M., and the following period beginning at 7:15 P. M. and ending at 7:15 A. M.

The first five days were used as a control period, in an attempt to estimate the status of body water. The subject received the constant diet, as already described, and was permitted to drink water freely. During the first two days there was considerable retention of body water, half of which was lost spontaneously in the following three days. There were no attacks during this period.

On days 6 and 7 the subject received 348 milli-equivalents of sodium (87 m.-eq. in the diet and 261 m.-eq. as sodium chlorid), administered daily, during the twelve hours while awake. For the first thirty-six hours there was a marked retention of water in the body. A very severe attack, as previously described, occurred at the height of hydration. During the following twelve hours there was a spontaneous loss of water with a distinct diminution in the severity of the symptoms. During the first twelve hours of day 8, the subject ingested 261 milli-equivalents of sodium (87 m.-eq. in the diet and 174 m.-eq. as sodium bicarbonate). Again, there was a marked hydration with a second attack occurring at its height. During the following twelve hours, all of the water which had been held during the preceding twelve hours was released and the subject again improved. It will be noted that these two attacks occurred when sodium was administered and retention of water by the body was in evidence. Consequently, one cannot assume that either one of these factors is solely responsible for the attacks.

In order to study separately the effect of sodium administration and retention of body water, the subject was purposely dehydrated during days 11, 12 and 13, by rigidly restricting the intake of water. When the subject was dehydrated to a level at which he had previously had no attacks (control period) he was then given 261 milli-equivalents of sodium (87 m.-eq. in the diet and 171 m.-eq. as sodium bicarbonate), during the first twelve hours of day 13. A severe attack occurred, in spite of the fact that the body contained strikingly less water than it did when the attacks were absent (days 1 to 6 and 9 to 11). During the first twelve hours of day 14, the same intake of sodium was maintained and water was freely given. There was marked retention of body water, although no attack was produced. However, the following day (day 15), during which the same intake of sodium was maintained, a fourth attack occurred, but not until the subject had lost approximately 500 grams of the water previously stored.

Beginning with day 16 and continuing to day 34, the intake of sodium was only that contained in the diet (87 m.-eq.). Water was permitted and averaged about 1,800 grams daily. Ammonium chlorid, an acid-producing salt, was administered in increasing dosage. At first, water was retained but this was gradually lost. During the period of water retention, it will be noted that the amount of water held was practically as great as when sodium was administered, but attacks resulted when sodium was given, while none were produced by ammonium chlorid. Since ammonium chlorid administration is associated with an increased excretion of sodium, it is presumed that ammonium chlorid failed to produce an attack because it prevented the retention of sodium by the body.

It is obvious from this data that attacks occurred quite independently of whether water was stored or lost by the body. Furthermore, attacks were produced by the administration of sodium, regardless of whether such administration was attended by hydration or dehydration. The acid-producing salt, ammonium chlorid, did not produce an attack, in spite of the fact that it was at first attended by a retention of body water quite as great as that accompanying ingestion of sodium.

SUMMARY.

It is assumed from our experiments that the symptoms of Ménière's disease are due to the retention of sodium by the body. If a sufficient supply of water is available it will likewise be retained, but this fact is not of primary importance. Apparently, the local tissues involved in Ménière's disease have either an increased avidity for sodium or an unusual sensitivity to it.

The therapeutic indications are: (1) to permit as small an intake of sodium as is possible and (2) to prevent the accumulation of sodium by the body. The former is easily attained by means of diet and the latter by the administration of acid-producing salts, such as ammonium chlorid. When these two factors have been controlled, the intake of water does not need to be considered.

We have treated fourteen cases of typical Ménière's disease successfully by this method. Each patient was carefully selected in an effort to rule out any obvious lesion, such as an acoustic nerve tumor or a suppurative process in the temporal bone, and every precaution was taken to eliminate psychical elements from this study.

While the number of patients is not large, it represents a group carefully chosen from the cases available in our clinic during the past ten months. Each patient was hospitalized for a period of thirty days or more and the efforts of two members of the staff and myself were directed daily towards a careful clinical and laboratory study of the problems at hand.

It is of extraordinary interest to note that identical results were obtained for all of the patients in this group. In not one instance did we fail to produce an attack by the administration of sodium, and not once were we disappointed in obtaining complete relief by the medical therapy above described. The patient whose chart is herein presented has been without a seizure since ammonium chlorid was first given to him on October 16, 1933, and similar results for shorter periods have been obtained for the remaining thirteen cases in the group.

We are fully aware that presumptuous claims for medical therapy cannot be based upon the meager statistics herein compiled. It is not our wish that such an inference should be drawn. Rather do we desire to suggest a new etiologic factor in the production of Ménière's disease and express the hope that it may lead to further research in therapeutics.

Obviously a study of this kind leads to many ramifications in the field of clinical medicine and physic and biochemistry. With each original discovery, new problems for further investigation are brought to light. Innumerable questions promptly arise and critical suggestions are prone to appear. Both are invited. We ask for criticism with the hope that it will criticise the work which is presented rather than the problems which the study suggests.

TREATMENT.

1. Protein, unrestricted or forced.
2. Calories, as indicated.
3. Low salt content.
4. Medication. Ammonium chlorid, 3.0 gms., with each meal, in capsules (six capsules each containing 7½ grains taken during the meal), three days on and two days off. The capsules should not be replaced by the chocolate coated or the enteric coated pills because the latter sometimes pass through the gastro-intestinal tract without being absorbed. The ammonium chlorid can be given in this dosage for an indefinite time without injurious effects. We have had patients with nephritis receiving ammonium chlorid in this manner for a period of five years.
5. Water intake unrestricted, although excessive quantities of liquids should not be taken.
6. Diet, approximate neutral, low sodium diet.

Group A: The following foods may be taken daily:

1. Eggs, meat, fish and fowl as desired.
2. Bread as desired.
3. Cereal, one of the following: Farina, oatmeal, rice, puffed rice or puffed wheat.
4. Potato and one or more servings of any of the following: (a) macaroni, (b) spaghetti, (c) rice, (d) corn, (e) cranberries, (f) prunes, (g) plums.
5. Milk as desired.
6. Vegetables and fruits daily of any fruit and of any vegetable not included in groups "B" and "C" as desired.
7. Butter, cream, honey, jellies, jams, sugar and candy permitted as desired.
8. Tea and coffee as desired.

FOODS TO BE AVOIDED.

Group B: All salt meats and fish, or bread, crackers and butter prepared with salt. Carrots, clams, condensed milk, raisins, caviar, cowpeas, olives, spinach, cheese, endive, oysters.

FOODS TO BE TAKEN NO MORE THAN TWICE WEEKLY.

Group C: Lima beans, beets, buttermilk, cantaloupe, cauliflower, celery, chard, dried cocoanut, dried currants, dates, figs, horseradish, kohlrabi, limes, muskmelon, peanuts, peaches, mustard, pumpkin, radishes, rutabagas, strawberries, turnips, turnip tops, watercress.

NOTE: All food to be prepared and served without salt.

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FACTORS CONTRIBUTING TO PHONEME RECOGNITION ABILITY OF USERS OF THE 22-CHANNEL COCHLEAR IMPLANT SYSTEM

MASAE SHIROMA, MA
TOKYO, JAPAN

KIYOSHI HONDA, MD
KANAZAWA, JAPAN

NOBORU YAMANAKA, MD
SAPPORO, JAPAN

JUN KAWANO, MD
TOKYO, JAPAN

KUMIKO YUKAWA, MD
TOKYO, JAPAN

KOZO KUMAKAWA, MD
TOKYO, JAPAN

SOTARO FUNASAKA, MD
TOKYO, JAPAN

A study was carried out to determine which factors contributed to the vowel and consonant recognition ability of recipients of the 22-channel cochlear implant system. On the basis of the statistical analysis, no isolated factor showed a strong correlation with vowel recognition score. On the other hand, negative correlations were found between patients' consonant recognition scores and postoperative psychophysical percepts such as threshold levels and maximum comfortable loudness levels. However, multiple regression analysis also showed that the combination of lower threshold levels, a larger number of usable electrodes, and wider dynamic ranges contributed to higher consonant recognition scores.

KEY WORDS — cochlear implant, multiple regression analysis, psychophysical percepts, vowel and consonant recognition.

With advances in technology, it has become possible for profoundly deaf people who receive minimal or no benefit from conventional hearing aids to obtain speech recognition ability through cochlear implant systems, single-channel or multichannel. The performance varies widely from system to system and even among recipients using the same type of cochlear implant prosthesis.[1-3] From clinical experience with Nucleus 22-channel cochlear implant patients, we have found that the results vary greatly for both the speech discrimination scores and also for the postoperative electropsychophysical testing from subject to subject, even though the conditions at operation, such as the full insertion of the electrodes, were similar.

Many factors may influence an individual's ability to make use of electrical stimulation. Several researchers have attempted in the past to identify predictors of auditory performance with cochlear implants. Mecklenburg and Brimacombe[4] report from their experience with the Nucleus cochlear implant system that variations of performance can be related to a number of factors: motivation, age, cause of deafness, age at onset and length of unaidable profound deafness, neural population reserve, synthetic processing ability, ability to use bimodal percepts, and so on. No one factor, however, has been shown to correlate significantly with communication skills. Recognizing that a combination of variables including nerve viability, cognitive skills, and implant design affect performance, Gantz et al[5] carried out statistical tests and found no strong predictor in isolation except the effectiveness of multichannel speech processing compared to single-channel. Similar results were found by Cooper[6] in regard to determining predictors by using the University College Hospital/Royal National Institute for the Deaf cochlear implant system.

These previous studies suggest that it is difficult to determine the factors that can predict the success of cochlear implants before implantation. We have observed that postoperative psychophysical percepts such as threshold level (T level), maximum comfortable loudness level (C level), and dynamic range may play important roles in speech recognition ability. The object of this study was to correlate these postoperative psychophysical percepts with the phoneme recognition abilities of implant patients.

METHODS

SUBJECTS AND SPEECH RECOGNITION TESTS

Nineteen postlingually deafened adults, 12 men and 7 women, who had used the 22-channel cochlear implant system for at least about 5 months were included in this study. Prior to the implantation, all of them had an average hearing loss of greater than 110 dB hearing level, and they scored zero on open-set speech discrimination tests. None of the patients received benefit from high-powered amplification. The subjects ranged in age from 38 to 66 years (mean, 49.7 years). The length of profound deafness varied from 0.3 to 35 years (mean, 6.3 years). The distribution of causes of deafness was as follows:

From the Department of Otolaryngology, Tokyo Medical College (Shiroma, Kawano, Yukawa, Funasaka), and the Department of Otolaryngology, Toranomon Hospital (Kumakawa), Tokyo; the Department of Electronics, Kanazawa Institute of Technology, Kanazawa (Honda); and the Department of Otolaryngology, Sapporo Medical College, Sapporo (Yamanaka); Japan.

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REPRINTS — Masae Shiroma, MA, Dept of Otolaryngology, Tokyo Medical College, 6-7-1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 160, Japan.

3 meningitis, 4 ototoxic drugs (dihydrostreptomycin), 9 progressive deafness, 1 trauma, 1 Meniere's disease, and 1 sudden deafness.

Vowel and consonant recognition tests were employed to examine patients' ability at phoneme recognition in a context-free condition. Vowel testing required identification of 30 randomized presentations of five Japanese vowels /i,e,a,o,u/ in an isolated format, instead of the consonant-vowel-consonant context, which does not appear in the Japanese phonetic system. The consonant testing required a similar decision among 14 Japanese consonants, 4 presentations for each in random order, in a vowel-consonant-vowel context with the vowel /a/. The consonants were /p,t,k,b,d,g,h,s,z,m,n,r,j,w/.

The patients were asked to identify each stimulus after it was presented by a female speaker, live voice, under the condition of hearing alone. There were two repetitions of each complete test, and the mean scores across the tests were used for statistical analysis. All of the testing was carried out in a small room with ambient noise levels of about 45 to 50 dBA. A hand-held microphone about 20 cm from the speaker's mouth was used.

SELECTED FACTORS FOR ANALYSIS

Selected factors for this study are as follows. The patients' age at implantation and duration of profound deafness were selected as individual physiologic factors. Postoperative psychophysical percepts with the cochlear implant such as T level, C level, average current level (median between T level and C level), dynamic range (range between C level and T level), and number of usable electrodes were selected as psychophysical factors. For this analysis, each factor was represented by the mean value calculated over the electrodes used. To obtain the T levels and C levels on each usable electrode, the patients were measured in the bipolar plus 1 mode with a pulse width of 205 microseconds, and the wearable speech processor was programmed with an F0F1F2 coding strategy. Processors and patients with other modes, different pulse widths, or other coding strategies were not included in this study. Every patient had electrodes of the Nucleus intracochlear implant fully inserted into the scala tympani at the time of operation. However, several patients were forced to use fewer electrodes in their program because of either uncomfortable sensations in the basal turn or malfunction of electrodes.

STATISTICAL METHOD

To correlate the recognition scores of the vowel and consonant tests with each factor, Pearson's correlation coefficient was calculated. Multiple regression was also conducted to find the combination of factors that contribute to performance. In the multiple regression, a stepwise analysis was done by using the results of vowel or consonant recognition tests as dependent variables and the selected factors as independent variables. Factors that were included in the stepwise analysis had to have an F value of greater than 4. Before applying those single and multiple regression analyses, we examined distributions of the data. When the data deviated from the normal distribution, a power or logarithmic transformation was used to normalize the distribution.

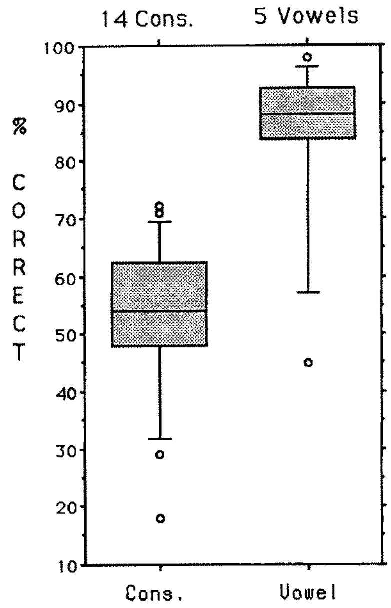

Fig 1. Vowel and consonant recognition scores. Line across middle of each box is median. Top and bottom of each box are 75th and 25th percentiles. Top and bottom of vertical lines (whiskers) are 90th and 10th percentile boundaries. Circles under and over whiskers are extreme values.

RESULTS

VOWEL AND CONSONANT RECOGNITION TESTS

The results of vowel and consonant recognition tests are shown in Fig 1 as box and whisker plots. The patients scored with an average accuracy of 52% (range, 18% to 72%) for consonants and 84% (range, 45% to 98%) for vowels. The majority of patients scored between 46% and 62% on the consonant test, and around 84% to 93% on the vowel test.

POSTOPERATIVE PSYCHOPHYSICAL FINDINGS

Figure 2 shows the distribution of results for the seven factors. Threshold level ranged from 66 to 150 digital units (du), with a mean of 112.7 du. The C level ranged from 135 to 180 du (mean, 158). The average current level ranged from 101.3 to 164.5 du, and the range of dynamic range was 16.5 to 69.5 du on a logarithmic current scale.[7] (The amplitude of the stimulus current generated in the cochlear implant may be varied from approximately 25 μA to 1,500 μA. This large current range is reduced to a manageable number of steps or digital units, from 1 to 239, by using a logarithmic transformation.) The number of usable electrodes ranged from 14 to 22 (mean, 19.6).

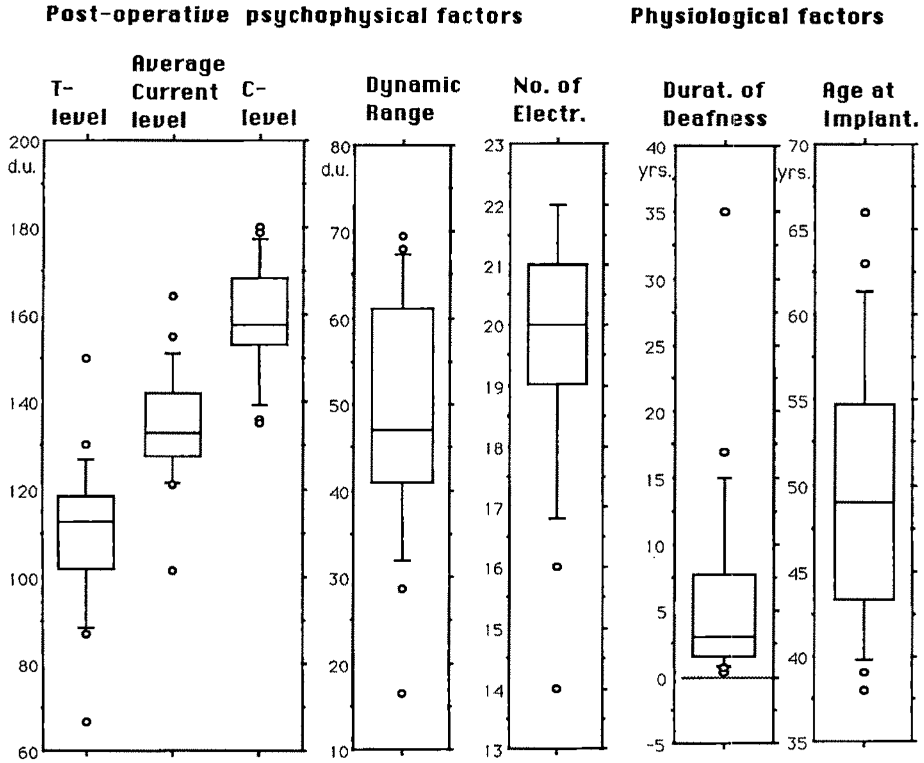

Fig 2. Box and whisker plots of selected factors.

The T level, average current level, C level, and dynamic range showed a nearly normal distribution. The majority of patients responded at around 101 to 118 du in T level, 153 to 168 du in C level, and 41 to 61 du in dynamic range. On other factors, the distribution deviated from normal. Although the number of usable electrodes ranged from 14 to 22, the distribution showed that the majority of patients used 19 to 21 electrodes. The duration of deafness ranged from 4 months to 35 years, although the median was 3 years. Age at implantation ranged from 38 to 66 years, and the median was 49 years. Data that showed a deviated distribution were transformed as follows: age at implantation, a squared number; duration of deafness, logarithmic transformation; and number of usable electrodes, fourth power transformation.

CORRELATION BETWEEN VOWEL AND CONSONANT RECOGNITION AND SELECTED FACTORS

Simple Correlation. The correlation coefficient of the vowel recognition score and each factor is shown in Fig 3A. No single factor showed a statistically significant correlation with vowel recognition scores. Average current level, T level, and C level showed a relatively strong negative correlation ($r < -.5$), which suggested that those who showed higher sensitivity to electrical stimulation scored high on the vowel recognition test. The correlation with the duration of deafness was negative, although not strong ($r = -.414$), indicating that the shorter the duration of deafness the better the vowel recognition. The number of usable electrodes and age at implantation showed a weak correlation.

The correlation coefficient between the consonant recognition scores and each factor is shown in Fig 3B. Both T level and average current level showed a strong negative correlation ($r < -.7$). There was a relatively negative correlation with C level. These results again suggest, for consonant recognition, that the better performers show high sensitivity to electrical stimulation. As with vowel recognition, a low negative correlation with duration of deafness was also observed.

With regard to the number of usable electrodes and dynamic range, although the correlation coefficients were not strong, the results suggest that patients perform better on the consonant recognition test when they have a wider dynamic range and a larger number of usable stimulus channels. The correlation with age at implantation was weak.

Multiple Regression. Multiple regression analysis was conducted by using the results of vowel or consonant recognition tests as dependent variables and the selected factors as independent variables. Because there was such a small range of vowel recognition scores with a deviated distribution, each patient's score was raised to the squared number for normalization. Two factors of average current level, the mean digital unit level of T level and C level, and the number of usable electrodes were included in the multiple regression model ($r^2 = .58$), and other factors were excluded. As stated before, the number of usable electrodes showed a weak correlation with vowel recognition in isolation, but was included in the multiple regression model. A complementary contribution of the number of electrodes to

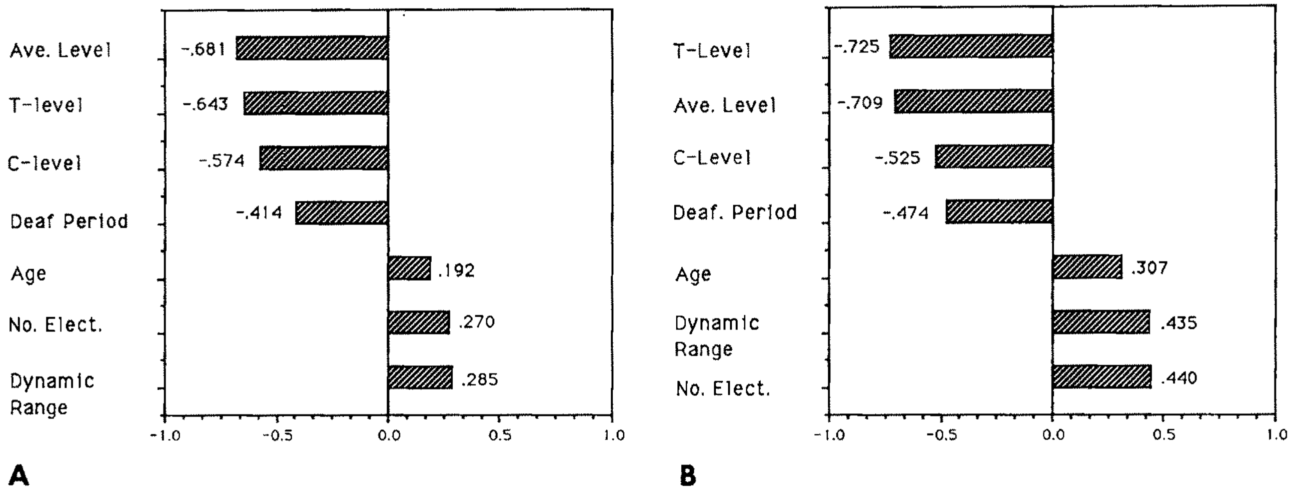

Fig 3. Correlation coefficients. A) For vowel recognition scores. B) For consonant recognition scores.

patients' electrical sensitivity was suggested. The same process was followed in a multiple regression analysis of consonant recognition. As a result, the T level, the number of usable electrodes, and dynamic range remained as factors that would be included in the multiple regression model. The correlation coefficient drawn from the analysis was .848.

From the above results, the following factors appear to contribute to vowel and consonant recognition ability: average current level and the number of usable electrodes for vowel recognition, and the number of usable electrodes and dynamic range for consonant recognition. Multiple regression equations for predicting patients' phoneme recognition are as follows. For vowel recognition score, the equation is

(1) $dv^2 = -.013 \times A + 3.85 \times (E/22)^4$

For consonant recognition score, the equation is

(2) $dc = -.008 \times T + .381 \times (E/22)^4 - .005 \times D$

The term dv^2 stands for the expected value of vowel recognition in a squared number, dc for expected value of consonant recognition, A for average current level, T for T level, D for dynamic range, and E for number of usable electrodes.

The scattergrams in Fig 4 show the relationships between the expected values of vowel and consonant recognition determined by the regression model and their observed values. In Fig 4A, the observed scores of the vowel test are distributed relatively homogeneously along the regression line, but some

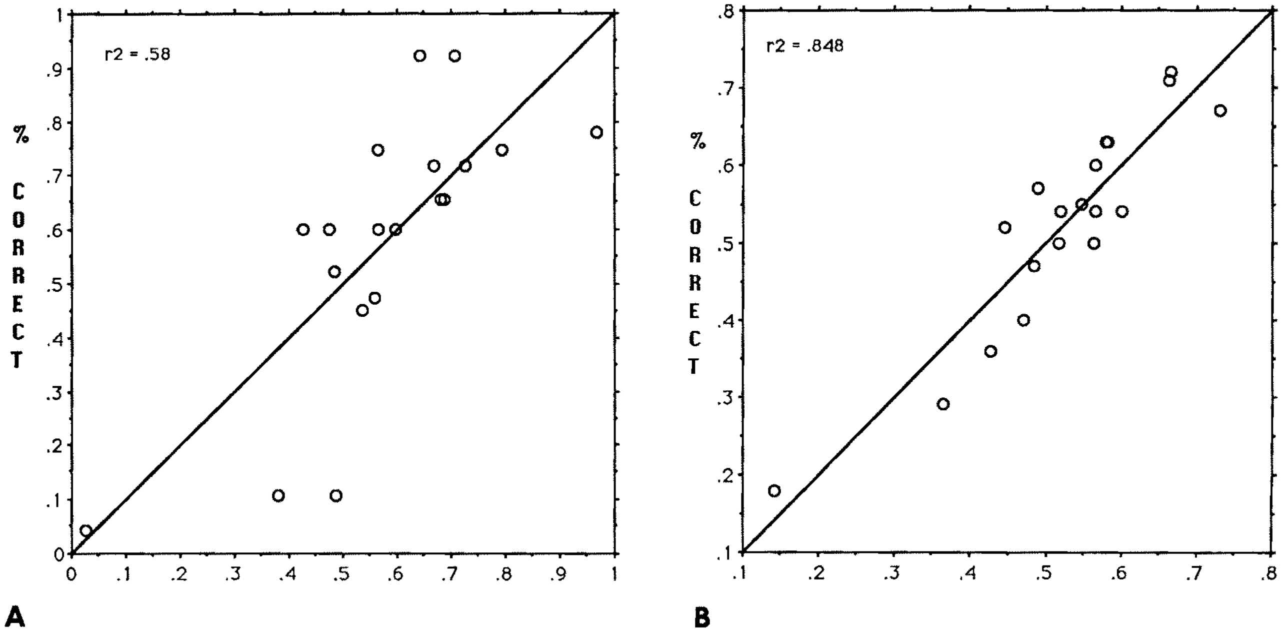

Fig 4. Expected values in relation to actual scores. Above and to left of regression line are scores of subjects who performed better than expected. Below and to right of regression line are scores of subjects who performed worse than expected. A) For vowel recognition. B) For consonant recognition.

data are apart from the line. This finding suggests that the prediction score for vowel recognition is not high for the possible predictive factors of average current level and the number of usable electrodes. On the other hand, in Fig 4B, the data are spread along the multiple regression line for consonant recognition. The results indicate that it is possible to predict consonant recognition scores by using a combination of T level, number of usable electrodes, and dynamic range.

DISCUSSION

Our study focused on possible contributing factors to the speech recognition ability of cochlear implant patients in a limited frame of vowel and consonant recognition.

A simple correlation analysis showed a relatively high negative correlation between patients' consonant recognition scores and current-related factors such as T level and average current level, but every factor showed weak correlation with vowel recognition scores.

The results of multiple regression analysis showed that the combination of T level, dynamic range, and number of usable electrodes could predict patients' consonant recognition ability. It also showed that a lower T level, a larger number of usable electrodes, and a wider dynamic range contribute to the improvement of patients' recognition of consonants. It was demonstrated that the ability to perceive consonants seems to be more dependent on electropsychophysical percepts than on age at implantation or length of deafness (that is, on the condition that the subjects were normal-hearing adults until they were deprived of hearing). As for vowel recognition, no combination of factors was found to predict performance. A probable reason for the low multiple correlation coefficient in vowel recognition is the concentration of performance scores at a high percentage.

In the consonant recognition test, those patients who had the combination of lower T level, wider dynamic range, and larger number of usable electrodes showed a higher score in our study. A lower T level with a wider dynamic range was considered to be related to sensitivity and function of the inner ear in terms of the population of remaining nerve fibers and their density, although the relation is not proved scientifically.

Like other researchers, we also carried out a comparative study between the results of a preoperative promontory stimulation test and the performance scores with the cochlear implant system with the aim of assessing the status of the auditory nerve and predicting the potential success of the implant. We found no relationship between T level and dynamic range and the promontory stimulation test, or between T level and dynamic range and postoperative psychophysical tests with the implant. What exactly causes low T levels remains unknown at present. Regarding neuronal survival, Otte et al[8] report that different causes of deafness result in different levels of neuronal survival in the cochlea. Our findings are inconsistent with their research, since some of our patients deafened by meningitis with lower T levels were high performers.

As for the number of usable electrodes as a possible factor in performance with the implant, Clark et al[9] and Holmes et al[10] also reported a positive correlation between the number of usable channels and performance. It seems natural to expect good speech recognition ability with a large number of stimulus channels, since the frequency resolution would be better for those patients.

Concerning the age at implantation, our results are consistent with other reports.[1,2,5,9,10] It does not appear to contribute to performance with the implant. The duration of profound deafness showed a negative correlation with implant performance, although not to the extent reported by Dowell et al[1] and Clark et al.[9] These two factors were not found in the multiple regression analysis to be predictive. This result may be due to the ambiguity of onset of profound deafness or the age at onset of deafness in many of the subjects.

The residual statistics in the multiple regression analysis are considered to be related to some other factors such as motivation and central processing ability. An Iowa group[5] reported that these factors could not predict audiological performance with an implant. They studied predictive factors by administering a battery of tests, including cognitive assessment, but found no single predictor. However, from clinical experience, it can be said that these factors seem to have an effect on performance. Further investigation is needed to define the factors that can predict postoperative performance with the implant system. Meanwhile, our findings from this study may be used as a guideline for counseling patients and for setting goals for rehabilitation.

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MANAGEMENT OF FLAP NECROSIS IN COCHLEAR IMPLANTATION

THOMAS J. HABERKAMP, MD
MILWAUKEE, WISCONSIN

MITCHELL K. SCHWABER, MD
NASHVILLE, TENNESSEE

Skin flap complications are the most commonly reported problems in cochlear implant surgery when the anteriorly based C-shaped flap is used for the incision. If the prosthesis is exposed by flap necrosis, local skin flaps may be used to obtain coverage. Unfortunately, the long-term viability of such flaps may be compromised by the pressure exerted by the transmitter. Two cases of flap necrosis severe enough to expose the prosthesis have been successfully managed by relocating the device to a position superior to the auricle, under healthy skin. In one case the receiver was removed owing to infection and reimplanted at a later date. In this case, the electrode array was left in place at explantation in order to stent the cochlea. The surgical techniques and flap designs for this procedure are presented. No further surgical complications have developed in either case. The devices are performing well for both patients at this time. We have found relocation of the implant a useful technique in the management of major flap necrosis. This technique may also be useful to prevent flap necrosis should excessive flap thinning occur during the implant operation.

KEY WORDS — cochlear implantation, flap necrosis.

INTRODUCTION

Cochlear implantation has become an increasingly common procedure in the rehabilitation of selected cases of profound deafness. Of the potential complications in cochlear implantation, the most frequently reported and potentially one of the most significant has been major flap necrosis, occurring in 4.8% of 459 cases as reported by Cohen et al.[1]

Local skin flaps have been most frequently used to obtain coverage of an exposed implant. However, several other alternatives can be used to manage these cases. Explantation of the affected ear and implantation of the opposite ear is possible, but is generally only used when no other alternatives exist. It is always preferable to save the other ear for future considerations such as advances in technology that may provide improved performance.

Another alternative is to keep the implant in the affected ear but to relocate the device to a site under healthy skin. Two cases are presented in which the device was moved to a more anterior site that was actually directly superior to the auricle. In both cases there were no further complications, and the device is still being successfully worn. These cases demonstrate an alternative to local skin flaps in the management of flap necrosis.

CASE REPORTS

Case 1. A 44-year-old woman underwent implantation on December 16, 1987. Her deafness was caused by a combination of multiple episodes of sepsis, which required ototoxic medications for treatment, and an intracranial abscess. An anteriorly based C-shaped flap was used, and a Nucleus 22-channel device was implanted. At the time of operation the flap was greater than 6 mm and was therefore thinned as recommended by the manufacturer.[2] This was felt to have contributed to the eventual flap necrosis. The flap was viable during the first postoperative week; however, by the second week, venous congestion was noted that progressed to obvious flap necrosis. Debridement of the necrotic tissue exposed the receiver of the implant (Fig 1A).

On January 27, 1988, the patient was taken to the operating room and the necrotic tissue was debrided, with both advancement and rotational scalp flaps used to cover the device. These flaps also became necrotic between 1 and 2 weeks postoperatively. A second attempt at coverage with local flaps was made on February 18, this time with a flap from the back of the neck. Although the flap once again looked viable for approximately 1 week, flap necrosis again developed between 1 and 2 weeks postoperatively. Because of chronic exposure of the device, it was felt that localized infection may have been contributing to the flap failures. Therefore, the patient was explanted on April 12. At the time of operation massive granulation tissue was found beneath the receiver. It was pushing the device laterally and had pulled the stay sutures through the bone to which they were secured. The granulation tissue did not extend to the mastoid. Because the infection was localized, the tail of the device was cut off and left in the cochlea as a stent. After the wound healed by secondary intention, the patient was reimplanted on July 27. The device was placed under an anteriorly based fasciocutaneous flap located above the ear (Fig 1B,C). There were no further complications and the wound healed well. The patient is a successful user at 3 years postoperatively (Fig 1D). She has 26% open-set speech discrimination abilities (NU-6) and can wear the

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From the Department of Otolaryngology and Human Communication, Medical College of Wisconsin, Milwaukee, Wisconsin (Haberkamp), and the Department of Otolaryngology, Vanderbilt University Medical Center, Nashville, Tennessee (Schwaber).

Presented at the Second International Cochlear Implant Symposium, Iowa City, Iowa, June 4-8, 1990.

REPRINTS — Thomas J. Haberkamp, MD, 9200 W Wisconsin Ave, Milwaukee, WI 53226.

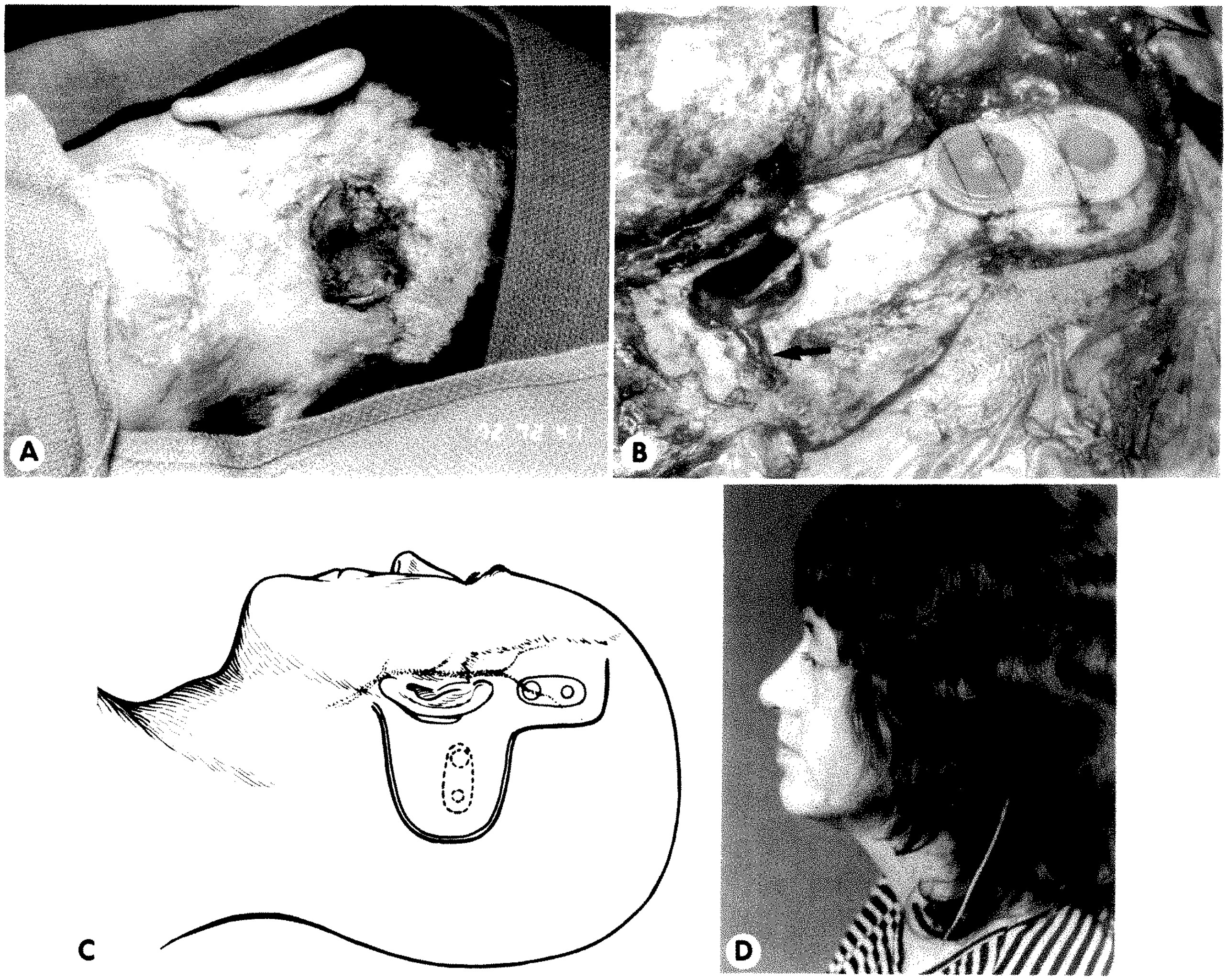

Fig 1. (Case 1) A) Nape of neck flap, rotated at previous operation, now demonstrates necrosis of distal tip. B) Receiver is shown in place above auricle following reimplantation. Bony channel for original device is shown (arrow). C) Schematic demonstrating original C-shaped flap, with L-shaped extension, used to relocate receiver above ear. D) Side view of patient showing excellent ability to camouflage external magnet.

device with standard magnet settings.

Case 2. An insulin-dependent diabetic underwent implantation with an anterior C-shaped flap. This flap was also thinned enough to expose hair follicles. The receiver was placed within 1.5 cm of the incision. By 6 weeks postoperatively, there was necrotic tissue over the receiver, and debridement of this tissue exposed the device.

The patient was taken to the operating room, where the wound was debrided and the flap fully elevated (Fig 2A). There was enough room within the flap to rotate the device 90°, bringing the device anterior-superior to its previous location, where it was then under healthy skin (Fig 2B). The device was cleaned with Betadine solution, but not removed. There were no further complications, and this patient is also presently a successful user.

DISCUSSION

Although not life-threatening, flap necrosis can be one of the most devastating complications of cochlear implantation, because the ability to keep a functioning implant in place is potentially jeopardized. The rates of major flap necrosis reported vary. Luxford and House,[3] in a report of 350 cases, found only 4 in which there was infection or failure of the incision to heal. None of these required explantation to resolve the problem. The rates of major flap necrosis reported with the Nucleus 22-channel device have ranged from 0% to 5.4%.[4,5] The majority of the wound problems in Cohen's[5] report occurred with the anteriorly based C-shaped flap, and therefore it has been suggested that the inferiorly based U-flap should be more widely adopted.[4] However, it was also noted in Cohen's report that 83% of flap problems occur within a surgeon's first three procedures. It appears that technical considerations such as flap thinning or placement of the device too close to the incision may play major roles in the rate of flap problems. Both of these considerations were noted in our cases and were felt to play central roles in the cause of the flap necrosis.

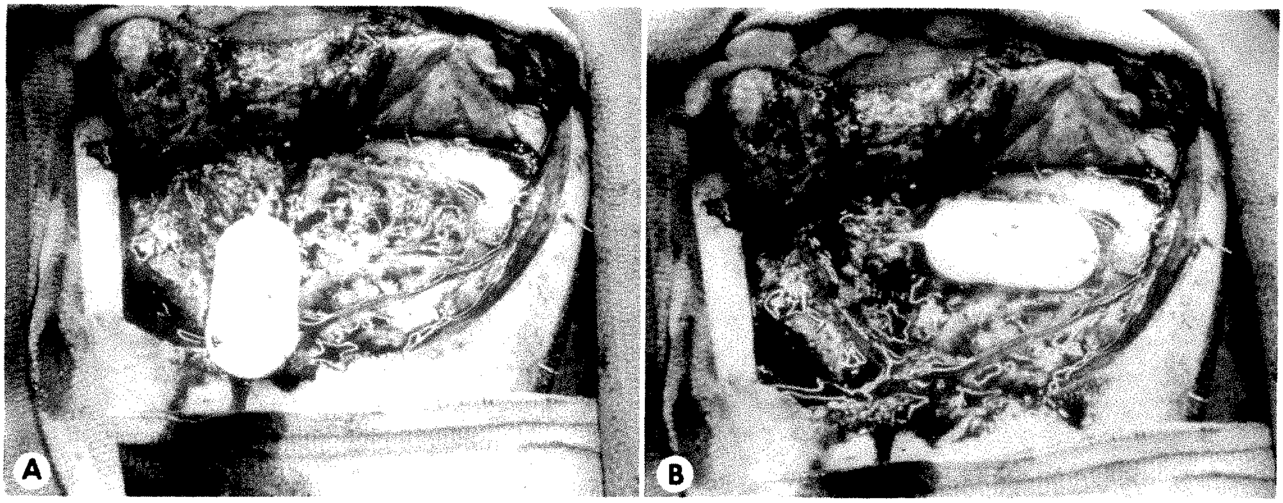

Fig 2. (Case 2) A) Posterior edge of device is immediately adjacent to incision, which has been reopened for exploration. B) After rotation, device now lies well within incisions.

The ideal management of flap problems is prevention. This can be accomplished by careful planning and execution of the flap operation. The receiver should be placed 1.5 to 2 cm from any incision. The receiver must be carefully located on a flat plane of the skull to prevent lateral pressure on the flaps. Finally, the flaps should only be carefully thinned, if at all, since excessive thinning will compromise the vascularity of any flap. If a surgical problem that jeopardizes the flap should occur during implantation, it would be better to move the device or modify the flap immediately than to allow necrosis to begin. Should the viability of the flaps be compromised in the postoperative period, hyperbaric oxygen therapy has been used to attempt to maintain viability.[6] We are not aware of any flaps that have been maintained with hyperbaric oxygen therapy alone. It should also be noted that a flap that was compromised enough to require hyperbaric oxygen therapy may not be able to withstand the long-term pressure of the magnet.

When flap necrosis results in exposure of the receiver, the key element in the management of this complication is to reestablish coverage of the receiver with healthy skin. The mainstay of treatment to date has been coverage with local skin flaps. In fact, this was attempted several times in case 1, with no success. At explantation, massive granulation tissue was found beneath the device, which displaced it laterally. It was felt that lateral pressure from the device caused the delayed flap necrosis.

Both these cases were successfully managed by relocating the device above the ear, where healthy skin was available. In case 2, there was enough room within the flap to allow the rotation within the original flap. Case 1 required a second flap above the ear (Fig 1C). In addition, the flap was raised as a fasciocutaneous flap, so there was blood supply from both the superficial temporal artery and the deep temporal artery, which supplies the temporalis muscle. As illustrated in Figs 1C and 3, this flap is theoretically compatible with the C- or U-shaped flap. The tail of the device does run under the incision when used with the U-shaped flap. However, the tail is located in a bony canal where it traverses the incision and will not place pressure on that incision.

Another theoretical disadvantage of this technique is that the receiver may be difficult to camouflage when located above the ear. This has not proven to be a cosmetic problem in women (Fig 1D), but may be more difficult in men if hair cannot be used to hide the device.

Finally, the case 1 patient also was temporarily explanted to allow resolution of the infection without the presence of a foreign body. Since the infected bed was able to be isolated from the middle ear, the tail of the device was left in the cochlea as a stent. This allowed for reinsertion of the implant at a later date. The reinsertion was accomplished without difficulties.

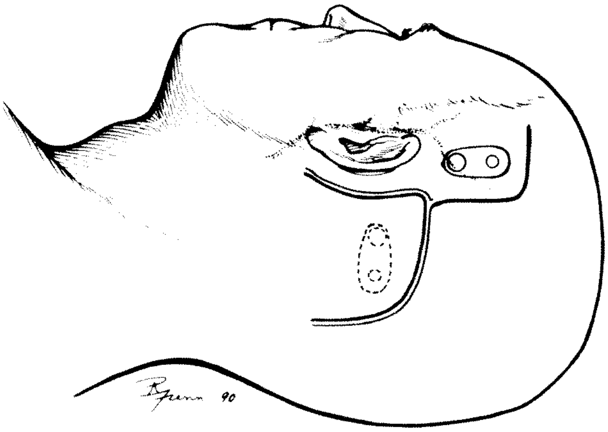

Fig 3. Schematic demonstrating how L-shaped flap could be used to place device if flap necrosis should occur with U-shaped flap.

Case 2 was managed successfully without the need to remove the electrode from the cochlea. The device was only removed in case 1 after several conservative attempts to control a resistant infection. It appears that the device can be saved in these cases if it can be isolated from the site of infection.

CONCLUSIONS

Flap necrosis is the most frequent complication of cochlear implantation. Thinning of flaps should be kept to a minimum if done at all to allow maximal blood supply to the flap. Since exposure of the device jeopardizes the ability to maintain the implant, it is vital to obtain coverage of the device with viable skin. We present an alternative technique to local flaps by relocating the device superior to the auricle under healthy skin. This technique may be used with the C-shaped or U-shaped flap, but may require creation of a second L-shaped flap. Additionally, when infection is present that requires explantation, the tail of the device can be left in the cochlea as a stent if it can be isolated from the infection. We also suggest relocating the device or redesigning the flaps if during implantation a technical problem occurs that may portend flap necrosis.

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NINTH SHAMBAUGH/SHEA WEEKEND OF OTOLOGY

The Ninth Shambaugh/Shea Weekend of Otology will be held March 6-8, 1992, at the Chicago Marriott Downtown in Chicago, Illinois. For further information, contact John J. Shea, MD, 6133 Poplar Pike, Memphis, TN 38119; Phone: (901) 761-9720; Fax: (901) 683-8440.

Ann Otol Rhinol Laryngol 101:1992

MODEL FOR UNDERSTANDING THE INFLUENCE OF SOME PARAMETERS IN COCHLEAR IMPLANTATION

CHRISTIAN BERGER-VACHON, MD, PHD
BACHIR DJEDOU, PHD
LIONEL COLLET, MD, PHD
ALAIN MORGON, MD

LYON, FRANCE

Considering the recognition performance obtained by an implanted patient, the authors have developed models to explain the decrease in performance when the number of open channels on the prosthesis is increased. The French cochlear implant Chorimac was used in this experiment. Two models have been developed. The first is monodimensional and the second is multidimensional. They respectively represent an increase in information and its superposition. Results suggest that for the patient, the superposition factor prevails and is detrimental to recognition. Its elimination should be a major goal. A good selection of electrodes in a relatively small number seems to be the best policy. This is already done in some cochlear implants. Some other parameters in the signal that seem worth being analyzed are introduced.

KEY WORDS — cochlear implant, electrode number, modeling, phonetic features.

INTRODUCTION

The evaluation of the possibilities open to a patient fitted with a cochlear implant is one of the questions submitted to the scientific and medical community. Some general propositions can be made,[1] but particular adjustments are needed to establish tests according to the particularities of the language, the levels of the patients, and the possibility for immediate testing during the rehabilitation.

When the performance of a patient is evaluated, the results depend more or less on three major factors: the patient, the phonetic material used for the test, and the prosthesis. Each of these factors can be widely discussed. For the patient, for instance, it is quite clear that a young person, highly educated, recently deaf, in whom the total deafness occurred after the acquisition of language, who has high motivation and good family support is a very good candidate. The quality of the rehabilitation will play an important part in the final result also.

The material used for the assessment will also influence the performance; to distinguish in a quiet environment sounds that are very different, with the help of speech reading, is obviously easier than coping with speech over the telephone, especially in an open context.

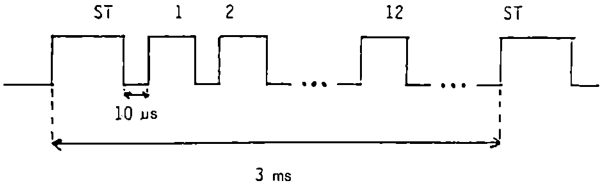

Fig 1. Diagrammatic representation of coding performed by Chorimac prosthesis.

The prosthesis plays a fundamental part in the transmission of the signal. Today, it is more or less agreed that the multichannel prostheses are better than the single-channel,[2] but the choice of the technology is still open for some patients. It is well known that the Nucleus or the Symbion implants, and even the Vienna/3M, have very enthusiastic supporters. In these cases, the coding of speech can be analog or digital.[3,4]

This paper is not meant to add to the series of results widely reported by the different teams, but is intended to explore some questions about the quality of signal processing, without any prejudice as to the further decisions that will be made for the patients.[5] It is based on an in-depth assessment performed with the collaboration of a very cooperative patient.

PATIENT TESTING

BASES OF ASSESSMENT

The three fundamental elements cited above will be discussed.

Patient. The subject of our experiments is a 54-

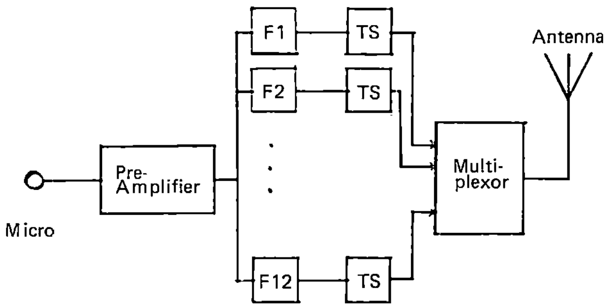

Fig 2. Representation of set of 12 pulses emitted by prosthesis.

From the Laboratoire "Audition et Voix" (URA 1447), Lyon (Berger-Vachon, Collet, Morgon), and the Laboratoire d'Electronique, Mesure et Instrumentation, Villeurbanne (Berger-Vachon, Djedou), France.

Presented at the Second International Cochlear Implant Symposium, Iowa City, Iowa, June 4-8, 1990.

TABLE 1. CHARACTERISTICS OF PROSTHESIS FILTERS

Filter	*Bandwidth*	*Central Frequency*
1	0- 240	120
2	240- 350	290
3	350- 450	395
4	450- 600	520
5	600- 800	690
6	800-1,250	1,000
7	1,250-1,450	1,370
8	1,490-1,850	1,660
9	1,850-2,500	2,160
10	2,500-3,500	2,960
11	3,500-4,900	4,150
12	4,900-7,500	6,050

TABLE 2. RECOGNITION PERCENTAGES

No. of Channels	*Logatomes*	*Vowels*	*Plosive-Fricative*	*Voiced-Unvoiced*
Patient				
1	28	73	96	64
3	31	71	93	63
5	12	57	36	61
7	17	43	40	84
Multidimensional model*				
1	23	53	82	51
3	31	58	83	60
5	48	63	83	91
7	63	86	78	78
Monodimensional model				
1	23	53	82	51
3	11	36	64	47
5	4	32	39	57
7	7	40	47	53
Monodimensional model including phase				
1	23	53	82	51
3	12	40	62	48
5	5	33	40	57
7	9	38	46	55

*With number of open channels increased.

year-old man who had been deaf for approximately a decade when he was fitted with a Chorimac cochlear implant in 1983 in the otorhinolaryngology department of Edouard Herriot Hospital of Lyon.

The patient is married and his family members provide very effective support. He was very willing to participate in our study; unfortunately, he rejected his implant in 1987 and the testing was halted.

Testing Material. For the purpose of the assessment a set of 12 logatomes was chosen[6] on the basis of analytical considerations of some basic features of the language. Three cardinal vowels were used (/a,i,o/), as well as a plosive-fricative opposition (/t/-/d/ and /s/-/z/) and the presence (/d,z/) or the absence (/t,s/) of voicing in consonants. This plan resulted in a 12-logatome set that was spoken in French: dada, dodo, didi, tata, toto, titi, sassa, sosso, sissi, zaza, zozo, and zizi. These logatomes were randomly repeated 10 to 12 times to produce lists of 129 words that were read to the patient.

Prosthesis. The Chorimac prosthesis[7] codes the signal in the following way. A set of 12 bandpass filters divides the speech spectrum. Then the energies detected by the filters are used to control the duration of constant-amplitude pulses. These pulses are distributed along the cochlea.

A diagrammatic representation of the data processing performed by the prosthesis is given in Fig 1. Every 3 milliseconds the prosthesis delivers a set of 12 pulses, shown in Fig 2. The filters have a logarithmic span in frequency. Table 1 gives the bandwidths of the filters and the corresponding mean frequencies.

Widely implanted by Professor Chouard's team in Saint-Antoine Hospital of Paris,[8] the Chorimac prosthesis has been used in many experiments, which are ongoing.

WORK WITH PATIENT

Preliminary Considerations. The channels of the prosthesis had been open and closed throughout the experiments, and the patient quickly pointed out that his auditory possibilities were different according to the number and the positions of the open channels. He was most satisfied with only a few channels open, in the middle of the range. This finding was the starting point of the experiment described in this paper.

Recognition Versus Number of Open Channels. Only seven channels could be used with the patient: 1, 7, 8, 9, 10, 11, and 12.

The 129-word lists were presented to the patient with the following arrangements of the channels:

1. 10.
2. 8, 10, 11.
3. 1, 8, 10, 11, 12.
4. 1, 7, 8, 9, 10, 11, 12.

The recognition performance is shown in Table 2. It can be pointed out that some increases in the number of open channels seem to be harmful to the recognition scores.

MODELING

DATA ACQUISITION

The duration of the pulses was recorded in the Laboratoire de la Communication Parlée in Grenoble, where a specific system was established to accurately obtain the data. (The duration was sometimes shorter than 1 microsecond.) A schematic of the system is shown in Fig 3. The duration of all the pulses produced during each utterance was stored.

The evolution of energy over time is represented in Fig 4. Two sets of pulses were selected to represent each logatome; the first was taken for the maximum of the energy of the first vowel (after smoothing), and the second is the minimum, corresponding

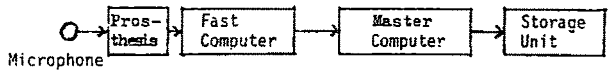

Fig 3. Schematic of system used for data acquisition.

to the second consonant.

Mathematically, each logatome was represented in a 24-dimensional space. In all, the pulses corresponding to two 129-logatome lists (L1 and L2) were recorded and characterized.

AUTOMATIC RECOGNITION

Multidimensional Model. The recognition of the utterances was performed through the comparison with the archetypes. The barycenters were taken for the archetypes of the classes of logatomes. They were computed from the first list (L1). A vector Bk with 24 coordinates represents the class (one is associated with each logatome) number k; Bk is the barycenter vector. The comparison is made through the use of a euclidean metric D(X,Bk) constructed between X and Bk (Fig 5). Each vector was classified to the nearest class. The recognitions computed when the number of open channels varies lead to the percentages given in Table 2. It is worth pointing out that the recognition performances are improved when the number of open channels is increased.

Monodimensional Model. This model is based on the supposition that the endolymphatic fluid remains totally depolarized during each set of 12 pulses. Consequent to this assumption, the information brought by the pulses was added in this model without reference to tonotopic organization at the ends of the auditory nerve. The vector X representing an utterance has only two coordinates: one for the vowel and one for the consonant. Each coordinate is the sum of the durations of the pulses given by the open channels. The results obtained with this model are given in Table 2.

Introduction of Phase. As the pulses do not arrive at the same time on the cochlea, a modification can be made in the former model by the introduction of information on phase. Consequently, the algebraic addition of the pulses was replaced by a vectorial sum (Fig 6).

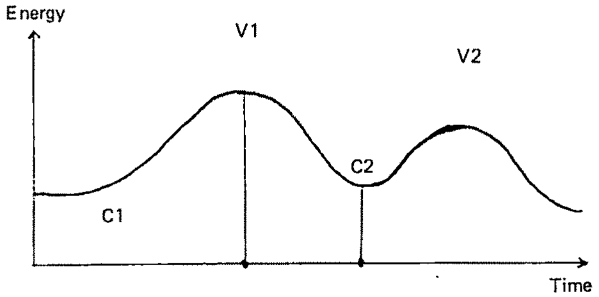

Fig 4. Evolution of energy over time. C1,C2 — first and second consonants, V1,V2 — vowels.

$$D(X,Bk) = \sqrt{\sum_{i=1}^{24} (Xi - Bki)^{2}}$$

Fig 5. Euclidean metric.

The phase is calculated according to the following formula:

(1) $\varphi i = 2 \times \pi \times Fi \times Ti$

where Ti is the delay of the i^{th} pulse, and Fi its central frequency. This sum is the reconstitution, according to the theory of Fourier, of the first sample of the signal. The results are shown in Table 2.

The similarity of monodimensional model results with or without phase must be emphasized. The improvement of the model is not followed by an increase in the recognition percentages. This fact could be a consequence of the monodimensional structure of the model.

INFLUENCE OF DIMENSION

The results indicate a clear difference between the behaviors of the monodimensional and multidimensional models.

If the sum on one dimension is considered, an early and dramatic fall in the recognition performance of the model is seen when the number of open channels is increased. This fall is worse than the decrease observed in the patient's performance. On the other hand, the increase found with the multidimensional model is quite different from the results we got with the patient.

In order to try to understand this behavior, a further experiment was done with the vowels and with the plosive-fricative feature. Channels 4, 6, 8, 10, and 12 only were used.

Multidimensional Model. Starting with the recognition scores given individually by the channels, the filters were associated in a "climbing" order (starting with the worst) and then in a decreasing order (starting with the best). The results given by

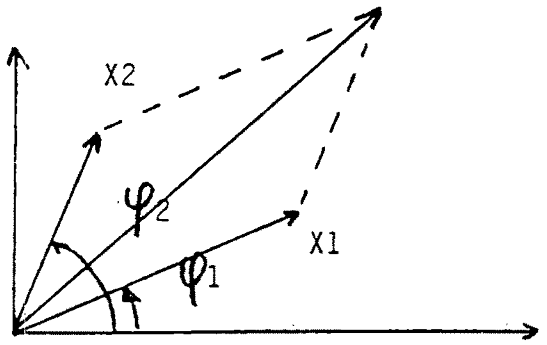

Fig 6. Vectorial addition of duration of two pulses.

TABLE 3. RECOGNITION PERCENTAGES OBTAINED WITH CHANNELS 4, 6, 8, 10, AND 12

No. of Channels	*Decreasing Order*		*Climbing Order*	
	Vowels	*Plosive-Fricative*	*Vowels*	*Plosive-Fricative*
Multidimensional model				
1	68	82	35	58
2	53	88	59	57
3	65	84	66	56
4	77	83	84	71
5	79	81	79	81
Monodimensional model				
1	68	82	35	58
2	69	87	36	50
3	46	70	37	47
4	49	64	50	47
5	43	57	43	57

these associations are shown in Table 3. These results confirm the former observations. Regarding the distinction between the plosive and the fricative features, the recognition score can hardly be improved, as the starting point with the best channel is already high.

Monodimensional Model. The results produced by this model are given in Table 3. The results obtained in decreasing order confirm the fall of the recognition scores. Nevertheless, it is possible to raise the performance when starting from a poor channel. The explanation is probably linked with the introduction of some good discriminatory information.

FUTURE DEVELOPMENTS

"Real" Model. It can reasonably be asserted that the two phenomena of superposition and tonotopy reside together in the cochlear duct. A general distance D taking into account the two metrics d1 (multichannel) and d2 (monochannel) taken previously would lead to interesting results close to the ones observed with the patient. Thus D should be written according to the following formula:

$$D = a1 \times d1 + a2 \times d2 \qquad (2)$$

where a1 and a2 are two weighting coefficients.

Noise. A statistical model considering variance is worth developing. The variance could be a way of introducing noise. The augmentation of the number of open channels increases the information, and increases the noise as well. We need to determine which phenomenon is prevailing. Furthermore, it is quite possible to develop monodimensional and multidimensional statistical models. From our first trials, it appears that performance decreases when the number of channels is increased by too much.

CONCLUSIONS

This work indicates that a large augmentation of the number of channels used in a cochlear prosthesis is not the best solution to increase the efficiency of the signal when the channels are used simultaneously. It seems better to have fewer but more carefully chosen channels. This result is quite clear in the case of the superposition of the channels.

This work suggests that it is a good policy to take the best channels in a relatively small number, and to avoid as much as possible the superposition of too much information. According to us, the choice of the best channels cannot be done independent of knowledge of the properties of speech and acoustics; this is another extension of this work.

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COMPLICATIONS OF PERCUTANEOUS ENDOSCOPIC GASTROSTOMY IN HEAD AND NECK CANCER PATIENTS

SHARON E. GIBSON, MD
BARRY L. WENIG, MD
JAMES L. WATKINS, MD
CHICAGO, ILLINOIS

Percutaneous endoscopic gastrostomy (PEG) has been shown to benefit patients with resectable carcinoma of the head and neck. In order to determine whether patients with existing tumor or postresection anatomic changes of the upper respiratory tract can undergo this procedure with an acceptably low complication rate, 349 patients with attempted PEG were studied. The PEG procedure was successful in 114 of 122 carcinoma patients, as compared to 220 of 227 patients in a control group (patients with neurologic disease). Intraoperative complications preventing PEG placement included pharyngeal or esophageal obstruction, inadequate transillumination of the abdominal wall, and respiratory distress and occurred in 7% of carcinoma patients and 3% of controls. The incidence of airway obstruction during endoscopy was equal between groups (1%). Postoperative complications related to the gastrostomy tube were more frequent in the non-head and neck cancer group (14% versus 5%). Younger age, fewer concomitant medical problems, and better nutritional status may account for this difference. These findings suggest that preoperative, postoperative, and unresectable head and neck cancer patients are appropriate candidates for PEG, and postgastrostomy performance appears superior to that in other patient populations.

KEY WORDS — complications, head and neck cancer, percutaneous endoscopic gastrostomy.

INTRODUCTION

Percutaneous endoscopic gastrostomy (PEG) has gained wide acceptance as a relatively safe and efficient means of enteral access.[1-4] Its use in the management of head and neck carcinoma has become a recent focus of attention in the otolaryngology literature.[5,6] While most agree that PEG is beneficial for selected cancer patients, opponents to its routine placement fear an unacceptably high complication rate, resulting particularly from impedance by a tumor mass and respiratory distress during endoscopic insertion.[6] Postgastrostomy complications, especially in patients receiving concurrent chemotherapy, have been reported as high as 16%.[2,4,7]

Our recent study of preoperative PEG in resectable carcinoma patients did not substantiate these concerns.[8] We observed no instances of airway compromise during 43 procedures and had a tube-related complication rate of less than 5%. These patients, however, comprised a select group of patients with primary, resectable malignancies of the head and neck.

This study was undertaken to determine whether candidacy for PEG applies to all patients with carcinoma of the head and neck, including those awaiting resection and those who have had resection as well as those with unresectable disease. Candidacy is based on an acceptable complication rate as compared with a control group with normal head and neck anatomy. As the literature to date demonstrates a surprisingly low postgastrostomy complication rate for head and neck cancer patients, we will also explore patient characteristics within each population that may account for this disparity.

MATERIALS AND METHODS

A retrospective analysis was performed of all patients undergoing PEG at the University of Illinois College of Medicine and affiliated hospitals between July 1988 and March 1991. Inpatient charts, tumor registry, and endoscopic reports were searched to document the primary diagnosis (reason for PEG), demographic characteristics, and outcome (success or failure to accomplish PEG). Concomitant medical disease was assessed by the number of failed or significantly impaired organ systems (cardiovascular, pulmonary, renal, hepatic, hematopoietic, or endocrinologic). Laboratory estimation of nutritional status by serum albumin and hematocrit at the time of PEG was recorded.

Patients with a diagnosis of squamous cell carcinoma of the head and neck were categorized by primary site, tumor stage, and disease status. Patients' disease status was designated as preoperative resectable, postoperative with no evidence of active disease, or unresectable. Previous or concomitant irradiation or chemotherapy, and its timing relative to PEG, was noted.

Patients undergoing PEG for non-head and neck carcinoma diagnoses comprised the control group. These included patients with inadequate oral alimentation due to altered mental status, chronic aspiration of central neurologic origin, neuromuscular dysphagia, and cachexia associated with disseminated nonsquamous malignancies.

The PEG was performed in all patients under lo-

From the Department of Otolaryngology-Head and Neck Surgery (Gibson, Wenig) and the Division of Gastroenterology, Department of Internal Medicine (Watkins), The University of Illinois College of Medicine at Chicago, Chicago, Illinois.

Presented at the meeting of the American Broncho-Esophagological Association, Waikoloa, Hawaii, May 5-6, 1991.

REPRINTS — Barry L. Wenig, MD, 1855 W Taylor St, Suite 2.42, Chicago, IL 60612.

TABLE 1. DISTRIBUTION OF HEAD AND NECK CARCINOMA PATIENTS BY SITE AND STAGE

	Larynx	*Tongue*	*Tonsil*	*Oral Cavity*	*Total*
Stage II	12	2	4	0	18
Stage III	10	7	7	11	35
Stage IV	17	14	19	11	61
Total	39	23	30	22	114

cal anesthesia with intravenous sedation (0.5 mg of Versed and 30 to 50 mg of Demerol). The operative procedure is performed as follows. With the patient in the supine position, a flexible fiberoptic gastroscope is introduced perorally and advanced to the region of the gastric fundus. Transillumination of the anterior abdominal wall by the gastroscope directs the point of sterile puncture. A silk suture is passed through the puncture site and grasped by the endoscope, which is then brought out through the mouth. A 16F to 22F rubber gastrostomy catheter is secured to the orally extruded suture and pulled into the stomach by withdrawal of the suture through the abdominal wall. The tube is stabilized by internal and external bolsters. Feedings are begun following the return of bowel function, generally within 24 hours of placement.

Failure to accomplish PEG within each group was documented. Reason for failure was attributed to pharyngeal or esophageal luminal obstruction preventing insertion of the gastroscope, inadequate transillumination of the abdominal wall to allow safe puncture, or intraoperative respiratory distress.

Gastrostomy-related complications, ie, those related to the indwelling catheter, were sought and documented. Possible unfavorable events included major (sepsis, pulmonary aspiration, abdominal wall breakdown) as well as minor complications (gastroparesis or ileus, cellulitis, chronic gastric leakage).

RESULTS

During the 32-month study period, PEG was attempted with 349 patients. Successful placement was achieved in 334, of whom 114 had existing or previous squamous cell carcinoma of the head and neck. The remaining 220 required PEG for primarily neurologic deficits.

The distribution by primary site and stage[9] of carcinoma patients with successful PEG is shown in Table 1. Of this group, 78 underwent PEG prior to primary resection, 13 postresection with no evidence of tumor, and 23 with unresectable disease. Twenty-six patients had received full-course primary or postoperative radiotherapy prior to PEG. Chemotherapy consisting of 5-fluorouracil and cisplatin for two or three cycles was administered within 3 months of PEG in 15 patients. Three received chemotherapy prior to PEG; 12 began chemotherapy immediately afterward.

TABLE 2. REASONS FOR FAILURE TO ACCOMPLISH PERCUTANEOUS ENDOSCOPIC GASTROSTOMY

	Carcinoma Group (n = 114)	*Neurologic Group (n = 220)*
Pharyngeal or esophageal obstruction	3 (2.6%)	1 (0.5%)
Inadequate transillumination of abdominal wall	4 (3.5%)	4 (1.8%)
Intraoperative respiratory distress	1 (0.9%)	2 (0.9%)
Total	8 (7.0%)	7 (3.2%)

TABLE 3. POSTOPERATIVE GASTROSTOMY COMPLICATIONS IN HEAD AND NECK CARCINOMA GROUP

	No. of Pts	*%*
Sepsis	1	0.9
Breakdown of abdominal wound	1	0.9
Ileus	1	0.9
Cellulitis	3	2.6
Total (n = 114)	6	5.2

Failure to accomplish PEG occurred in eight patients in the head and neck carcinoma group (7%) and seven in the neurologic group (3%). Reasons for failure in each group are listed in Table 2. The incidence of intraoperative respiratory distress was equal between groups at 1%.

Following successful PEG, six head and neck cancer patients (5%) experienced gastrostomy-related complications (Table 3). No cases of aspiration or hemorrhage were observed. The patient in which abdominal wound breakdown occurred had completed three cycles of chemotherapy 30 days before PEG insertion.

Postoperative complications related to gastrostomy occurred in 31 patients (14%) of the neurologic group, as listed in Table 4. Massive pulmonary aspiration was seen in 3 patients, resulting in respiratory failure in all 3 and death in 1. Leakage of gastric contents, which was not seen in the carcinoma group, was chronic in 15 neurologic patients.

Patient characteristics with possible bearing on gastrostomy-related complications are summarized in Table 5. Demographics include an age range for the carcinoma patients of 33 to 87 and a range of 41 to 90 for the neurologic group. The male-to-female ratio was approximately 5:1 for head and neck can-

TABLE 4. POSTOPERATIVE GASTROSTOMY COMPLICATIONS IN NEUROLOGIC GROUP

	No. of Pts	*%*
Sepsis	1	0.5
Massive aspiration	3	1.4
Ileus	2	0.9
Breakdown of abdominal wound	4	1.8
Cellulitis	6	2.7
Gastric leakage	15	6.8
Total (n = 220)	31	14

TABLE 5. PATIENT CHARACTERISTICS

	Carcinoma Group	*Neurologic Group*
Average age (y)	55	68
No. of organ systems compromised	1	3
Hematocrit (%)	37.8	28.2
Serum albumin (g/dL)	3.5	3.0

cer patients and 7:3 for the control group. Serum albumin (normal values, 4.0 to 5.5) and hematocrit (normal, 40.0 to 50.0) were decreased in both groups, but to a greater degree in the neurologic group. Statistical significance between the two groups, however, was not reached for either variable.

DISCUSSION

Gastrostomy has become the preferred means of alimentation for patients with chronic dysphagia and aspiration. The Stamm gastrostomy, in which concentric pursestring sutures are placed through the adjacent gastric musculature and mucosa, was introduced in 1894[10] and remains in use today. Associated problems including gastric leakage and tube dislodgment led to the development of permanent mucosal-lined gastrostomies, of which many modifications have been described.[11] Reported complication rates with these procedures range from 15%[12] to 24%.[13] Major morbidity includes wound dehiscence, peritonitis, and hemorrhage and is largely related to the laparotomy required for these gastrostomies.

The need for an open abdominal procedure has been virtually eliminated by the development of percutaneous gastrostomy placed via endoscopic visualization.[1] The PEG is performed routinely under local anesthesia. It is easily tolerated by patients with normal aerodigestive tract anatomy and carries an acceptably low risk of intraoperative complications in this population.[14]

For patients with head and neck carcinoma, the ability to undergo PEG and its associated risks is of special interest. The distal gastrointestinal tract is usually intact and therefore amenable to enteral feedings. Dysphagia and aspiration from an existing tumor mass, postresection anatomic alteration, or mucositis from adjuvant irradiation and chemotherapeutic regimens frequently prevent oral alimentation. The relative comfort, ease of management, and availability for long-term or intermittent use make gastrostomy a desirable means of enteral access for these patients. In addition, rehabilitation of speech and deglutition can proceed without the hindrance of a nasogastric tube and with nutritional supplementation as needed. It is therefore important to determine whether patients with head and neck cancer are good candidates for PEG.

Postgastrostomy problems with gastroparesis, chronic leakage, abdominal wall cellulitis, or breakdown and sepsis have occurred in up to 16% of patients following PEG performed for neurologic debilitation.[2,4,7] Pulmonary aspiration after PEG has been reported in 36% of neurologically compromised patients,[15] carrying a significant risk of mortality. In contrast, the observed gastrostomy-related complication rate in our initial study of patients undergoing primary resection of head and neck carcinoma was less than 5%.[8] Shike et al[5] found a similarly low incidence in their cancer population in which the mean length of gastrostomy-dependent alimentation was 135 days. One case of aspiration pneumonitis was noted in their series. This disparity of complication rates between the head and neck cancer patients and those with neurologic indications for PEG is reaffirmed in the current study. Five percent of the carcinoma group experienced postgastrostomy problems. Half of these had local cellulitis at the puncture site that resolved with enteral antibiotic therapy. Only 1 patient developed a major complication, sepsis, requiring parenteral antibiotics and feedings. Similar complications were seen in the neurologic group, but at a significantly higher rate (14%). In addition, massive aspiration with subsequent pulmonary failure occurred in 3 patients. Chronic gastric leakage, a complication not observed in the head and neck cancer patients, was recorded in 15 patients in the neurologic group.

These differences may be based on the more debilitated state of patients with advanced neurologic disease. The number of accompanying failed organ systems parallels the increased age in the neurologic group. Patients with concomitant peripheral vascular disease and metabolic or endocrinologic aberrations (eg, diabetes mellitus) have impaired wound healing and may be predisposed to development of chronic leakage or cellulitis at the catheter site. Similarly, malnutrition contributes to poor tissue integrity, local wound breakdown, and infection. Although both patient groups demonstrated low hematocrit and serum albumin values, those in the neurologic group were more severely depressed.

The incidence of gastrostomy-related complications in patients receiving chemotherapy is an important issue. Cytotoxic agents, often given in combination with radiotherapy, commonly cause mucositis of sufficient severity to prevent adequate oral nutrition, forcing patients to rely significantly on enteral supplements. Unfortunately, the fear of neutropenia and thrombocytopenia leading to bleeding, cellulitis, chronic drainage, or sepsis has prompted some authors to condemn PEG in the perichemotherapeutic period. We found only 1 of 15 patients undergoing full-course chemotherapy within 3 months of PEG placement to develop wound breakdown, and it did not progress to sepsis and responded to local care. No episodes of temperature elevation, bleeding, or overt sepsis were noted in this group. On the basis of these observations, we cannot support the routine rejection of all patients on a chemotherapeutic protocol from candidacy for PEG. Further studies involving larger patient numbers and specific determination of platelet and white blood cell counts are needed to more accurately predict whether certain patients are at an unacceptably high risk for this procedure.

In the analysis of unsuccessful attempts at PEG, the failure rate was higher for the head and neck cancer patients than those in the neurologic group (7% versus 3%). These rates are in agreement with those in the existing literature, in which PEG was unsuccessful in 4% to 7% of attempts for all patient populations.[3,4,6,16] In both groups, inadequate transillumination of the abdominal wall was responsible for half of the placement failures. This was attributable to many factors, including anatomic alteration from previous gastrointestinal surgery, high-riding stomach (beneath an elevated left hemidiaphragm), and morbid obesity. As other patients with similar features underwent PEG uneventfully, poor outcome cannot adequately be predicted preoperatively from these findings alone.

Any contraindication to PEG in the head and neck cancer population therefore lies in the inability to successfully pass the gastroscope to the gastric fundus. This may arise in two situations: luminal narrowing with a diameter too small to accommodate the endoscope, and intraoperative respiratory distress. Obstruction of the upper aerodigestive tract may occur at the level of the oral cavity, oropharynx, hypopharynx, or esophagus and may be due to tumor bulk, irradiation fibrosis, or postoperative changes. Advanced laryngeal lesions may also obscure the cricopharyngeal inlet. In our study population, 61 of 114 patients had stage IV cancer, and only 1 with a tonsillar lesion involving the lateral and posterior walls failed PEG because of obstructing tumor. Another patient had a concomitant esophageal carcinoma that prevented passage of the gastroscope. Of 14 patients with surgical alteration of the head and neck, one had a prohibitive pharyngeal stricture. An additional 26 patients underwent PEG successfully following full-course radiotherapy; this finding suggests that irradiation-induced fibrosis does not generally hinder placement. Overall, 3% of our carcinoma patients failed PEG because of oropharyngeal or esophageal luminal obstruction regardless of preoperative, postoperative, or unresectable disease status. Empirically, only patients with tumors involving the pterygoid musculature with severe trismus preventing peroral admittance of the endoscope should be routinely excluded as candidates for PEG.

Intraoperative respiratory distress is a valid concern for head and neck cancer patients when instrumentation is performed in the presence of a marginal airway. The routine administration of narcotics and sedatives prior to endoscopy certainly predisposes to this complication. Hunter et al[6] advocate deferral of PEG until after tracheotomy or resection when managing posterior pharyngeal and pyriform sinus lesions.

In this study, 9 carcinoma patients had a preexisting tracheotomy or laryngostoma at the time of PEG. In the remaining 105, PEG was attempted without a secured airway. This group included 19 patients with stage IV pharyngeal lesions and 13 with advanced (stage III or IV) pyriform tumors. One patient who had stage IV disease of the tonsil experienced respiratory distress intraoperatively. The risk of intraoperative complication with PEG for advanced lesions therefore does not appear prohibitive. In fact, airway compromise occurred with identical frequency in the neurologic group (1%). Although no mass impingement on the respiratory tract occurs in this group, altered mental status with poor airway protection and impaired clearance of secretions lead to respiratory decompensation. Judicious administration of sedation is therefore crucial in all patients.

CONCLUSIONS

Patients with preoperative or unresectable carcinoma of the head and neck, as well as those who have had resection, are candidates for PEG. The failure rate for endoscopic placement was 7%, as compared to 3% in controls undergoing PEG for neurologic disease. However, only half of the failures in the carcinoma group were due to pharyngeal or esophageal obstruction. The incidence of respiratory distress during PEG with advanced tumors did not exceed that of the control group.

Head and neck cancer patients demonstrated a significantly lower rate of postgastrostomy complications (5% versus 14%), which may be attributed to younger age, better nutritional status, and fewer concomitant medical problems within this group. These findings indicate that the risk of complications with PEG is not prohibitive in head and neck cancer patients, and indeed they appear superior candidates for PEG as compared to our control group.

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7TH WORLD CONGRESSES FOR BRONCHOLOGY & BRONCHOESOPHAGOLOGY

The 7th World Congresses for Bronchology & Bronchoesophagology will be held Sept 28-Oct 2, 1992, at the Mayo Clinic and Mayo Medical Center in Rochester, Minnesota. For further information, contact Udaya B. S. Prakash, MD, Secretary-General & Director, 7th WCB & WCBE, East-18, Mayo Clinic, Rochester, MN 55905.

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COMPARISON OF NEW TELESCOPIC VIDEO MICROLARYNGOSCOPIC AND STANDARD MICROLARYNGOSCOPIC TECHNIQUES

EIJI YANAGISAWA, MD
KEN YANAGISAWA, MD
JAY B. HOROWITZ, MD
LAWRENCE J. MAMBRINO, MD

NEW HAVEN, CONNECTICUT

A new approach to microlaryngeal surgery using a specially designed video microlaryngoscope with a rigid endoscopic telescope and an attached video camera was introduced by Kantor et al in 1990. The ability to video document and perform surgery of the larynx by viewing a high-resolution television image was demonstrated. This method was recommended over the standard microscopic technique for increased visibility with greater depth of field, unimpeded instrument access, instant documentation, and superior teaching value. The authors tried this new method and the standard microscopic technique at the same sitting on a series of patients. This paper will compare these two different techniques and discuss their advantages and disadvantages. Although the new method has many advantages, the standard microscopic technique remains as a valuable method in laryngeal surgery.

KEY WORDS — Kantor-Berci video microlaryngoscope, standard microlaryngoscopy, video microlaryngoscopy.

INTRODUCTION

With the introduction of a surgical microscope to endoscopic laryngeal surgery by Kleinsasser et al[1] in the late 1960s, microscopic laryngoscopy came of age.[2] Microscopic laryngoscopy has since become the standard method for endoscopic surgery of the larynx. The use of a video camera for microlaryngoscopy was introduced by Strong[3] in 1970 and thereafter advocated by Tardy and Tenta,[4] Strong,[5] and others.[6] Loré[7] advocated the use of a telescope for subglottic and anterior commissure lesions. Loré stated that the combination of telescope with an optical biopsy forceps eliminates the microscope and affords precise visualization of the microlaryngoscopy procedure.

At the 1990 Combined Otolaryngological Spring Meetings in Palm Beach, Florida, Kantor et al[8] introduced an ingenious approach to microlaryngeal surgery using a completely new video microlaryngoscope equipped with a rigid telescope and an attached video camera. The ability to video document and perform surgery of the larynx by viewing a high-resolution television (TV) image was demonstrated. They stated that this new method provides a magnified high-resolution image without imposing the microscope between the operator and the patient; affords surgeons easier access for instrumentation as well as giving greater depth of field; allows for instant documentation; eliminates the need to reposition or refocus the operating microscope while presenting a better view of the anterior commissure; and is the ideal method of choice in teaching microlaryngeal surgery.

The authors tried the Kantor-Berci video microlaryngoscopic technique and compared it with the standard microscopic technique at the same sitting on a series of patients. The purpose of this paper is to report the authors' experience with these two different techniques and discuss the advantages and disadvantages of each.

MATERIAL AND METHOD

Subjects. Because of the delayed availability of the Kantor-Berci videolaryngoscope system, the number of subjects was limited. Twenty-four consecutive patients who underwent microlaryngoscopy from July 1990 to January 1991 were studied. Eleven were men and 13 were women. The ages ranged from 28 to 79, with a mean age of 53. On all 24 patients, both the new Kantor-Berci video microlaryngoscopic technique and the standard microlaryngoscopic technique were tried at the same sitting. The distribution of disorders of the 24 patients was as follows: polyps (12 cases), carcinoma (2 cases), papilloma (2 cases), cysts (3 cases), granuloma (2 cases), hyperkeratosis (2 cases), and laryngocele (1 case).

Equipment. The following equipment was used for this study: 1) a Kantor-Berci video microlaryngoscope (Karl Storz 8590 VJ) with a specially designed telescope (Karl Storz 8575 A; total length, 17.7 cm; proximal aperture, 2.7 x 1.9 cm; middle aperture, 2.6 x 2 cm; distal aperture, 1.6 x 3.4 cm; Figs 1 and 2); 2) an Elmo EM 202 micro charge-coupled device (CCD) color video camera (Fig 2; used with a Karl Storz C-mount adapter) and a Karl Storz

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From the Section of Otolaryngology, Department of Surgery, Yale University School of Medicine (E. Yanagisawa, Mambrino), the Department of Otolaryngology, Yale–New Haven Hospital (Horowitz, K. Yanagisawa, Mambrino), and the Section of Otolaryngology, Department of Surgery, Hospital of Saint Raphael (E. Yanagisawa), New Haven, Connecticut.

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REPRINTS — Eiji Yanagisawa, MD, 98 York St, New Haven, CT 06511.

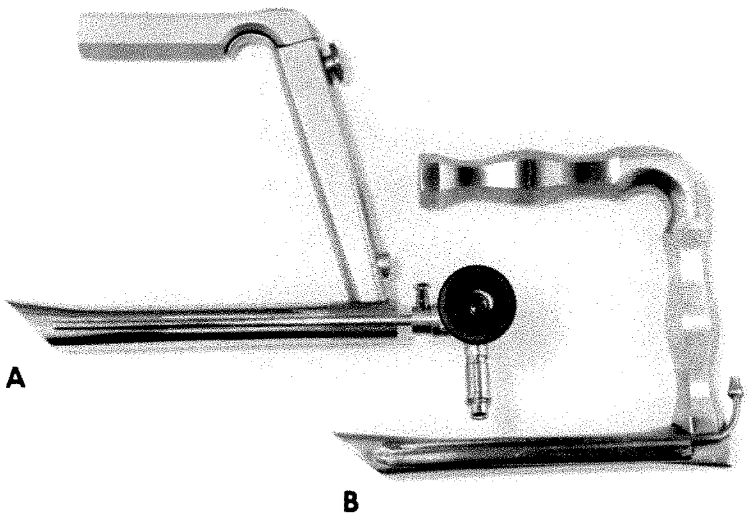

Fig 1. Microlaryngoscopes. A) Kantor-Berci video microlaryngoscope. B) Dedo laser microlaryngoscope.

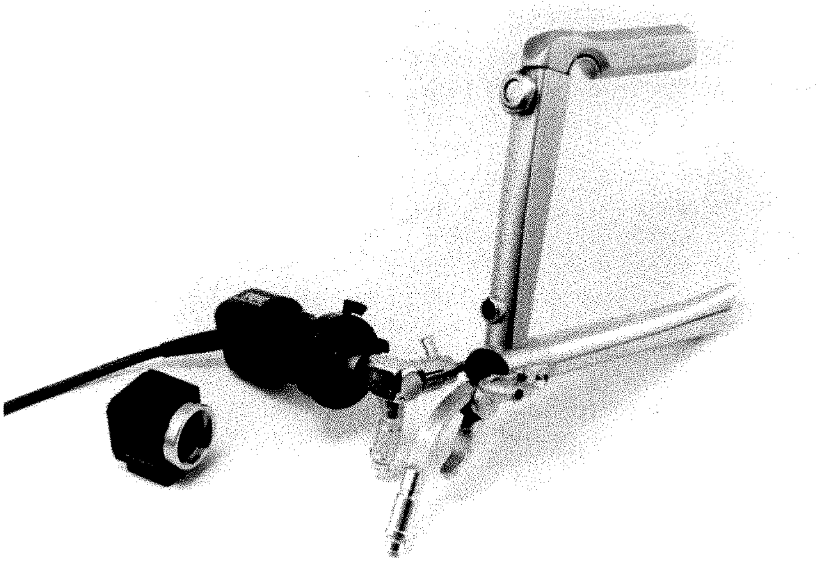

Fig 2. Kantor-Berci video microlaryngoscope with attached Karl Storz Supercam 9050B micro CCD camera. Elmo EM 202 micro CCD camera (left) also used in this study.

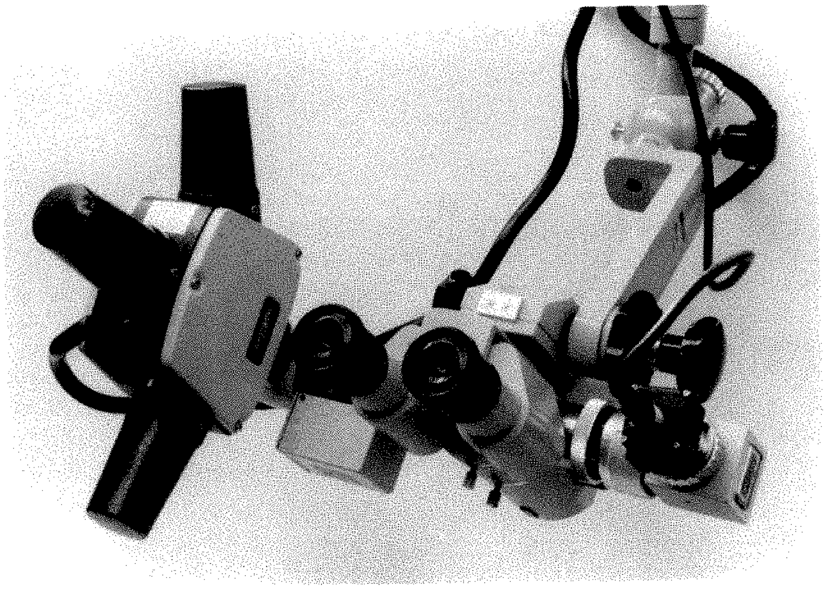

Fig 3. Hitachi DK5050 three-tube camera mounted on left side of beam splitter of Zeiss operating microscope. All microscopic images shown in this paper were taken with this camera.

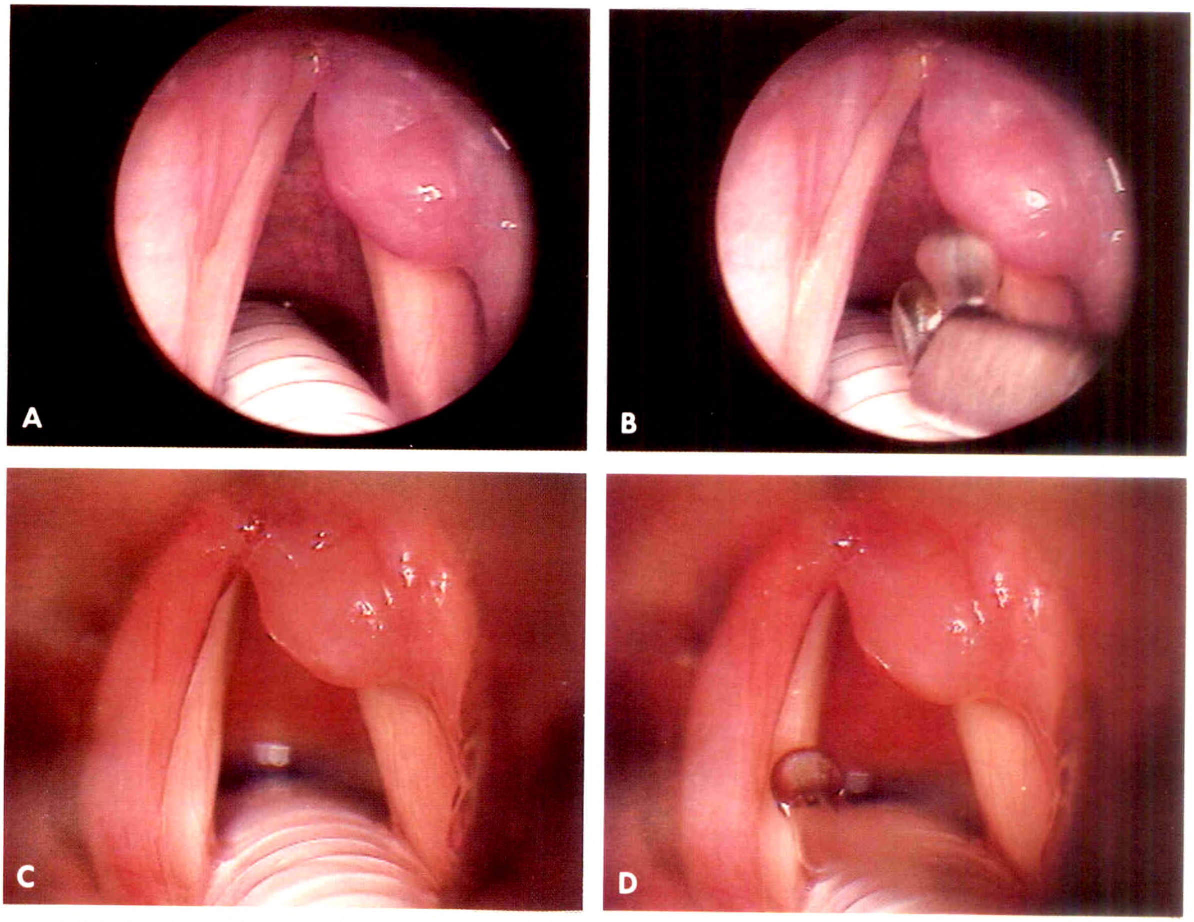

Fig 4. Supraglottic fibroma. A,B) Telescopic views (taken with Karl Storz Supercam). Note sharply focused cup forceps and its shaft in B. C,D) Microscopic views (taken with Hitachi DK5050). Note sharply focused cup forceps with blurred shaft in D.

Supercam micro CCD color video camera (9050B; Fig 2), which has a built-in adapter for a telescope; 3) xenon light sources (Karl Storz 487C and 615); 4) a Zeiss operating microscope with a beam splitter and an adapter for a microscopic video camera (Fig 3); 5) a Dedo laser microlaryngoscope (Pilling 52-2228; total length, 17.6 cm; proximal aperture, 2.1 x 2.1 cm; middle aperture, 1.5 x 2.5 cm; distal aperture, 1.4 x 3.0 cm; Fig 1); 6) a Pilling Luminator 2X; 7) a Hitachi DK5050 three-tube camera (Fig

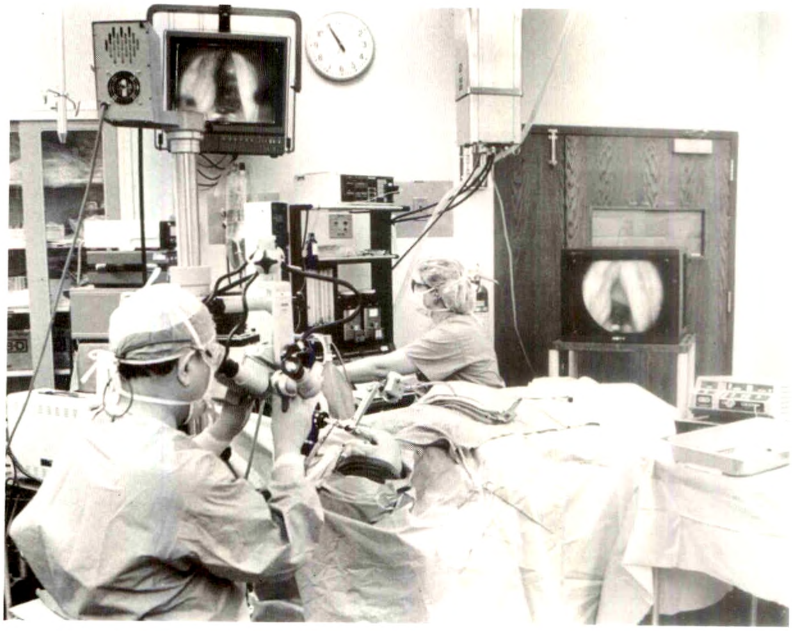

Fig 5. Technique of simultaneous telescopic and microscopic video microlaryngoscopy. Monitor 1 (right middle) shows telescopic view. Monitor 2 (left top) shows microscopic view.

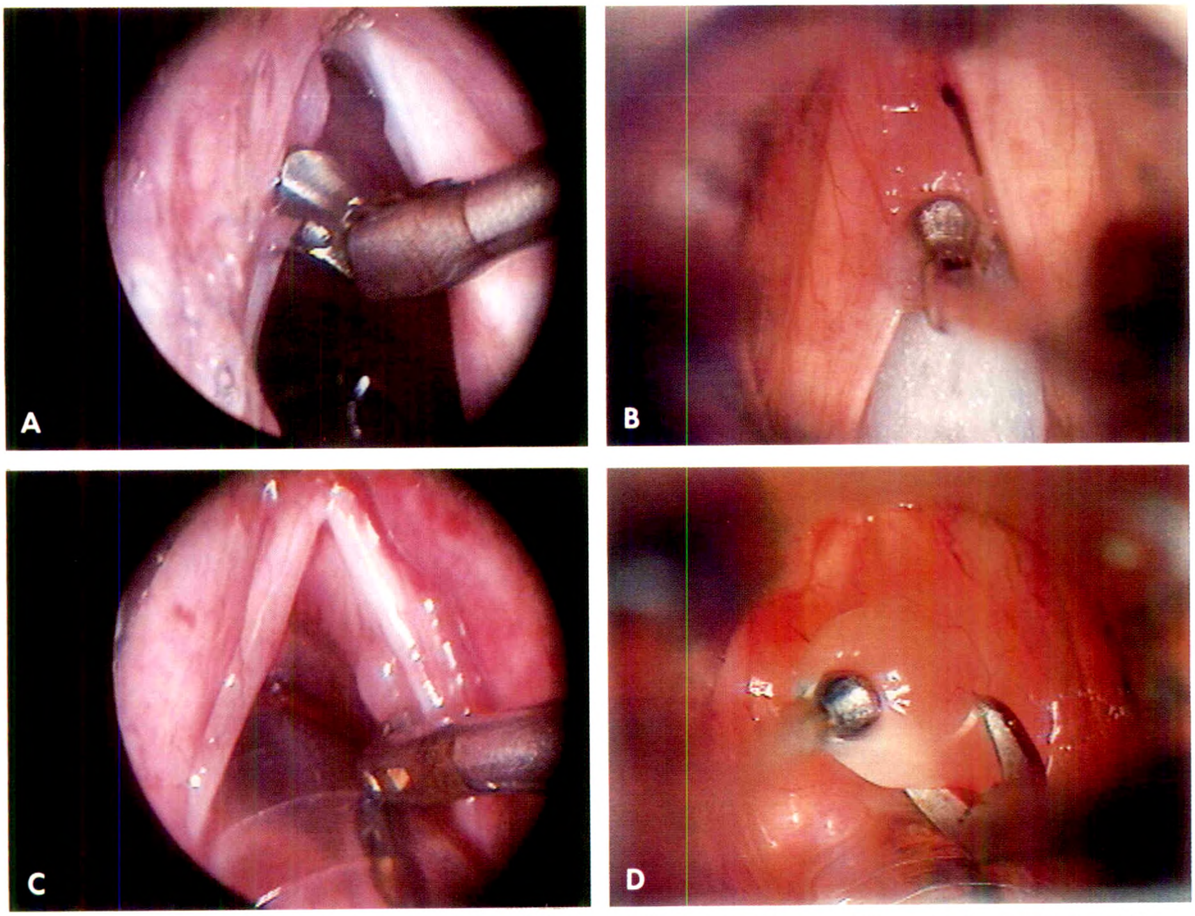

Fig 6. Instrumentation. A) Telescopic view (taken with Elmo EM 202). Papilloma on left true vocal cord grasped with forceps. B) Microscopic view. Papilloma on left vocal cord grasped with forceps (same patient as in A). C) Telescopic view (taken with Elmo EM 202). Polyp on right true vocal cord grasped with forceps obstructing view of polyp. D) Microscopic view. Large polyp being grasped with cup forceps and excised with microscissors (bimanual instrumentation).

3); 8) two Sony VO 5600 video recorders; 9) two Sony 19-in color monitors; and 10) a Sony UP-5000 color video printer.

Techniques. Under general anesthesia by means of a No. 6 endotracheal tube, the patient was prepared for microlaryngoscopy in the supine position. First, the Kantor-Berci laryngoscope was passed, positioned, and suspended by means of the Lewy laryngoscope holder. An Elmo EM 202 or a Karl Storz Supercam micro CCD color video camera was attached to the telescope, which had been inserted into the telescope channel built into the left sidewall of the Kantor-Berci microlaryngoscope (Fig 2). The telescope was then connected to the xenon light source (Karl Storz 487C or 615) by using a light cable. After the optimal exposure of the larynx was obtained, video recording was started. The entire surface of the vocal cords, particularly the anterior commissure, was examined well. Mucus, if present, was suctioned out. Laryngeal lesions were carefully examined and palpated with a microcup forceps. After adequate video recording was made, the Kantor-Berci laryngoscope was removed. Figure 4A,B shows telescopic images of a laryngeal lesion obtained by the Kantor-Berci system.

The Dedo laser microlaryngoscope was then passed into the larynx and suspended by using the same laryngoscope holder. The microscope, to which the Hitachi DK5050 three-tube camera was attached, was brought in and the larynx was examined. Laryngeal lesions were manipulated with the same equipment used for the Kantor-Berci system. The necessary biopsy or excision of the laryngeal lesions was then made. The entire procedure was video recorded. Figure 4C,D shows microscopic images of a laryngeal lesion obtained by the standard microscopic system.

After the video recordings had been compiled, they were critically reviewed by all the authors. Each examination was evaluated for technical ease on the basis of the amount of time and the number of attempts needed to obtain the optimal view of the larynx. Instrumentation difficulty, degree of visualization, image quality, and documentation value were assessed and assigned a score of 1 to 4.

In the last five patients, both telescopic video microlaryngoscopic and standard microscopic techniques were simultaneously employed by using the Kantor-Berci video microlaryngoscope (Fig 5). The

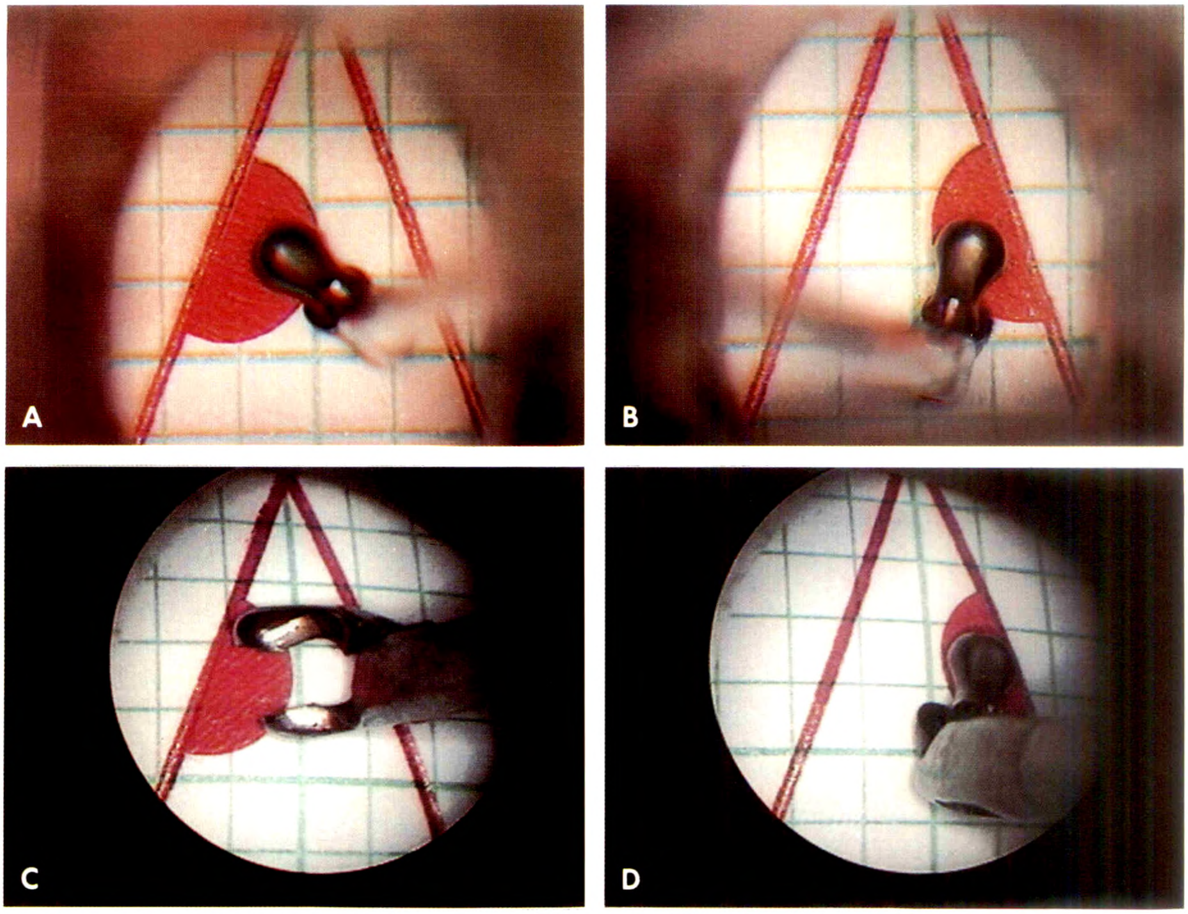

Fig 7. Instrumentation and visualization. A) Microscopic view. Simulated left-sided vocal cord polyp being removed with cup forceps. B) Microscopic view. Simulated right vocal cord polyp grasped with cup forceps. Note unobstructed view of polyp. C) Telescopic view (taken with Karl Storz Supercam). Simulated left vocal cord polyp being grasped with cup forceps. Note distortion of square grids in background. D) Telescopic view (taken with Karl Storz Supercam). Simulated right vocal cord polyp being grasped with cup forceps. Note obstruction of view of polyp by cup forceps resulting from telescopic lens positioned at lower end of laryngoscope lumen on left side.

Kantor-Berci videolaryngoscope was first passed, and the image obtained by a miniature CCD video camera was projected on monitor 1. By using the same Kantor-Berci videolaryngoscope, the larynx was examined with the Zeiss operating microscope, to which the Hitachi DK5050 three-tube video camera was attached. The microscopic image was projected on monitor 2. Laryngeal examination and surgical procedures were recorded. A synchronized dual image master tape was generated and used for comparative study.

RESULTS

Comparison of the telescopic and microscopic techniques was made from the standpoint of ease of laryngoscope insertion, ease of instrument manipulation, degree of visualization, image quality, and documentation.

Laryngoscope Insertion. Twenty-four patients underwent the Kantor-Berci video microlaryngoscopic technique and the standard microlaryngoscopic technique using the Dedo laryngoscope. The insertion of the Kantor-Berci scope was unsuccessful in three patients and difficult in four patients. Insertion difficulty was primarily due to the large size and straight outer contour (without an hourglass narrowing in its middle portion) of the Kantor-Berci laryngoscope and the unfavorable oral anatomy of the patients. Insertion of the Dedo laryngoscope for the microscopic technique was unsuccessful in one patient and difficult in another.

In one patient, who had a full set of teeth and a short neck with an anteriorly placed larynx, neither the Kantor-Berci laryngoscope nor the Dedo laryngoscope could be passed. The procedure became possible by the use of the hourglass-shaped Holinger anterior commissure 17 H laryngoscope, which was passed through the lateral oral approach. A small anterior commissure lesion could be visualized and removed by using a telescope passed through the Holinger laryngoscope.

Instrumentation. With the microscopic system, the increased distance between the surgeon and the patient made the insertion of instruments into the laryngoscope awkward and intraluminal bimanual instrumentation sometimes difficult. In the absence

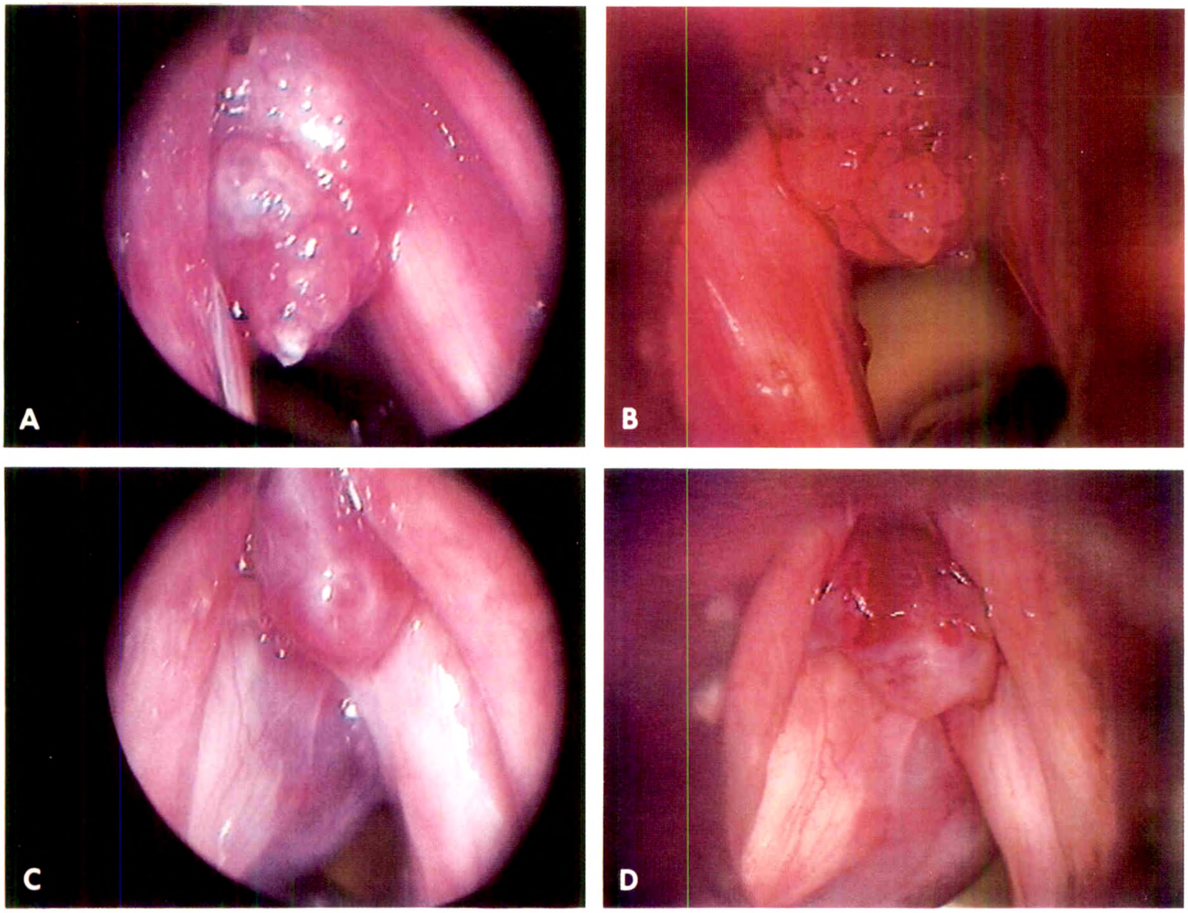

Fig 8. Visualization of anterior larynx. A) Telescopic view (taken with Elmo EM 202). Papilloma arising from anterior commissure of right true vocal cord (technically difficult case). Note excellent view of anterior end of tumor. B) Microscopic view. Same papilloma as shown in A. Note that anterior extent of tumor could not be seen. C) Telescopic view (taken with Elmo EM 202). Multiple polyps arising from anterior third of right true vocal cord, left true vocal cord, and subglottic region. D) Microscopic view. Same polyps as shown in C, showing sharply focused polyps arising from anterior third of right true vocal cord, left true vocal cord, and subglottic region.

of the microscope, instrument insertion was made easier with the telescopic system. However, instrument manipulation within the Kantor-Berci laryngoscope was not always easy — particularly horizontal movement. Instrument movement (the handle of forceps) toward the left while working on the right laryngeal lesion was limited because of the telescopic housing at the proximal opening of the laryngoscope on the left side (Fig 2).

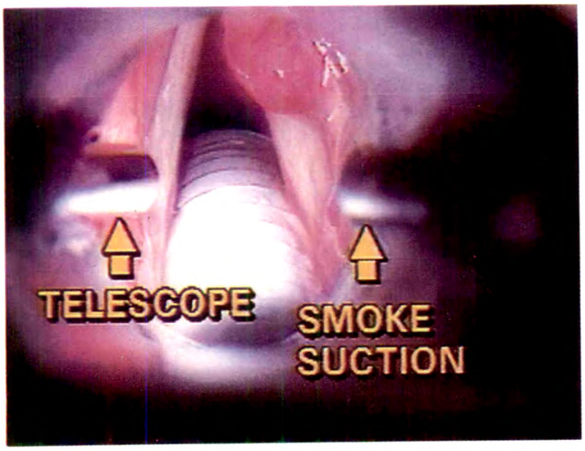

Fig 9. Inside lumen of Kantor-Berci video microlaryngoscope (taken with Hitachi DK5050). Note that telescope lens is situated at distal portion of laryngoscope lumen on left side. Note also suction (air or oxygen) attachment on right side.

With the Kantor-Berci system, the instrument could not be seen as it was being passed through the laryngoscope until it passed the tip of the telescope. With the microscopic system, the instrument could be seen during its passage, although it was out of focus (Figs 6B and 7A,B).

With the Kantor-Berci system, the telescope permitted extended visualization of the anterior anatomy of the larynx that was hidden by the laryngoscope blade (Fig 8A). Accordingly, the anterior hidden sites could not be reached with a straight forceps, necessitating the use of a specially designed angulated forceps.

The telescope on the Kantor-Berci system lies in a channel along the left side of the laryngoscope, while the smoke evacuator (air or oxygen connector) attachment is on the right side (Fig 9). These

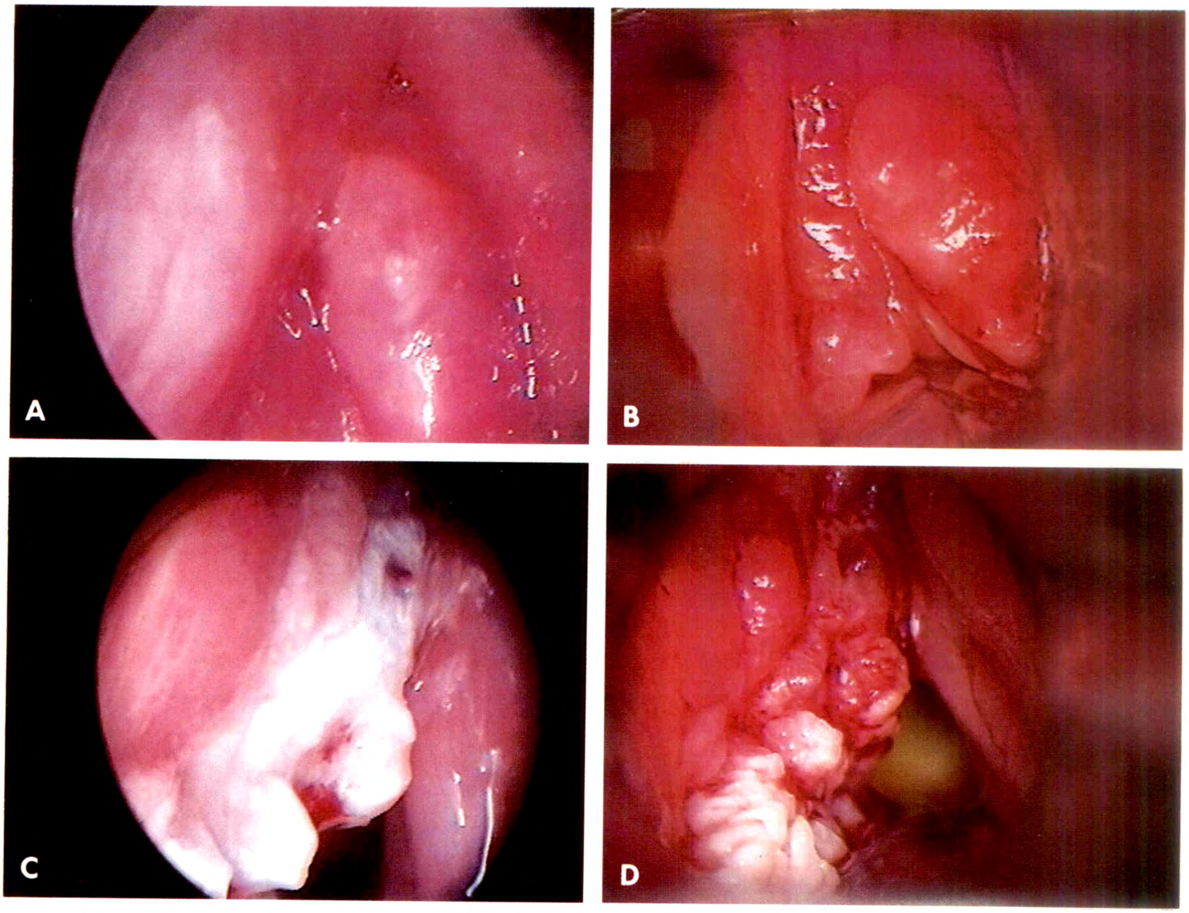

Fig 10. Visualization. A) Telescopic view (taken with Elmo EM 202) showing anterior polypoid mass. Posterior half of larynx could not be seen. B) Microscopic view of same patient as shown in A (taken with Hitachi DK5050), showing well-exposed polypoid masses along entire course of vocal cords on both sides. C) Telescopic view of verrucous carcinoma of left vocal cord showing only anterior half of tumor (taken with Elmo EM 202). Posterior one third could not be visualized. D) Microscopic view of same patient as shown in C, showing entire extent of tumor arising from true and false cords (taken with Hitachi DK5050).

attachments interfered with the movement of instruments during bimanual instrumentation microlaryngeal surgery.

Visualization. With the Kantor-Berci technique, we were unable to visualize the anterior commissure in three patients. The anterior commissure was poorly visualized in four patients (Fig 10A). The difficulty was due to the size of the laryngoscope in relation to the patient's anatomy. With the Dedo laryngoscope we were unsuccessful in visualizing the anterior commissure in one patient, while exposure was poor in three others (Fig 8B). In all of these cases of poor exposure of the anterior commissure, the procedure became possible when the anterior commissure was visualized by applying digital pressure over the thyroid cartilage.

In the majority of cases, we were able to visualize the entire surface of the vocal cords with both systems (Figs 4 and 6). However, with the Kantor-Berci system, visualization of the entire surface of the vocal cords was not possible in three patients and was difficult in six others (Fig 8A,C). The difficulty was considered to be due to the design of the Kantor-Berci video microlaryngoscope, which was built with a special emphasis on examining the anterior larynx. When the fixed-focus video camera was used, the larynx could not be examined (zoomed out) under lower magnification. This meant visual sacrifice of the posterior larynx in favor of the anterior anatomy (Fig 8A,C). With the Dedo laryngoscope we were unable to visualize the entire surface of the vocal cords in one patient and encountered difficulty in four others (Fig 8B,D).

With the microscopic technique, the larynx could be examined and operated on at 6x, 10x, 16x, 25x, and 40x magnifications (Fig 11). The ideal-size image was obtained when the magnification of the Zeiss operating microscope was set at 25x by using a 400-mm focal length lens (Figs 4C,D; 6B,D; 8D; and 10B,D). With the Kantor-Berci technique, different magnifications became possible with the use of the Karl Storz Supercam 9050B camera, although the magnification range was limited as compared to microscopic magnification (Fig 11A-C). The dials for zooming and focusing were stiff and somewhat difficult to adjust during the operation.

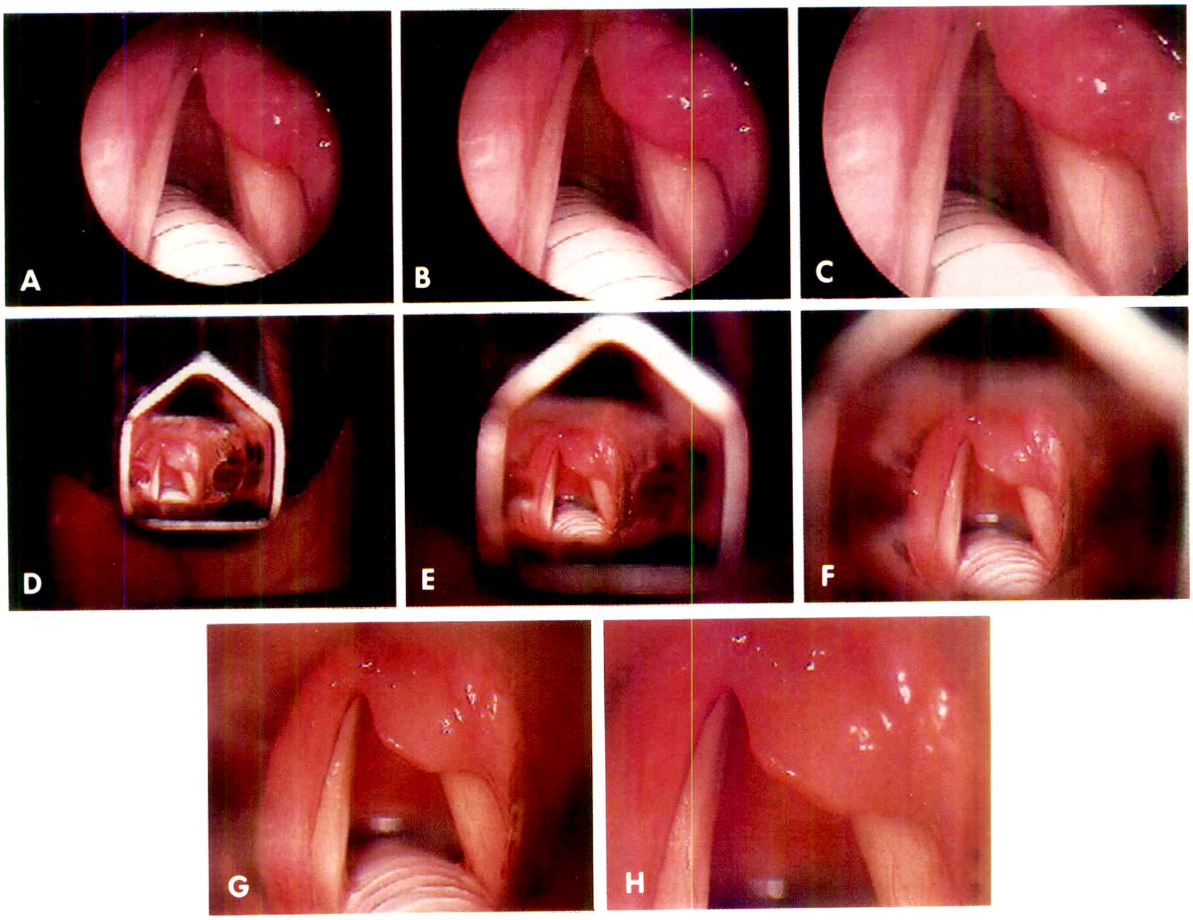

Fig 11. Magnification. A-C) Telescopic view of supraglottic fibroma taken by Karl Storz Supercam at A) low, B) middle, and C) high magnifications. D-H) Microscopic views of same supraglottic fibroma taken with Hitachi DK5050 at different magnifications (original x6, x10, x16, x25, and x40, respectively).

With both microscopic and telescopic techniques, it was necessary to refocus at different magnifications. With the microscopic technique, both vocal cords received equal amounts of illumination from the distal ends of the fiberoptic light carriers on both sides of the Dedo laryngoscope (Pilling 52-2228), as well as from the microscope light. Because of the position of the telescope and light source on the left side of the Kantor-Berci laryngoscope, left-sided lesions were well illuminated during instrumentation (Figs 6A and 7C), while the view of right-sided lesions was occasionally obscured by the instruments (ie, shaft of forceps; Figs 6C and 7D).

Image Quality. High-quality images were obtained with both the Kantor-Berci system and the microscopic system (Figs 4, 6, 8, and 10). Depth of field and resolution of images obtained with the Kantor-Berci technique were consistently better than those obtained with the microscopic technique (Figs 4A,B, 6A, and 8A). With the Kantor-Berci technique, all the objects, including the instrument and its shaft, the true and false vocal cords, the subglottic area, and even the inflated endotracheal tube and cuff, were in focus (Figs 4A,B and 6A,C). With the microscopic technique the depth of field was shallower; however, the object could be focused sharply at any given plane, such as the true vocal cords (Figs 4C,D and 6B,D). The cup of the forceps grasping the laryngeal lesion could be focused well, although its shaft was out of focus or not visible (Fig 6D). The depth of field of the microscopic view was often deeper than expected (Figs 4C,D and 8D).

Both systems produced excellent color quality. The images obtained by the Kantor-Berci system were somewhat bluish in color (Fig 8A,C), while those produced by the microscopic system had an orange tint (Fig 8B,D). The difference in color was considered to be due to the temperature difference between the xenon light source used with the Kantor-Berci system and the tungsten bulbs used with the microscopic system.

With the Kantor-Berci system, there was some distortion of the image because of the small size and position of the telescope attached to the lower left end of the laryngoscope (Figs 7C,D and 9). Although the visual field was somewhat limited, the microscopic system produced very little distortion of image (Fig 7A,B). On careful examination, some asymmetry of visual fields was noted, as demonstrated on the square grids in the background of the simulated telescopic view (Fig 7C,D). Note the symmetry of the background grids of the simulated microscopic view (Fig 7A,B).

Documentation. Video images obtained with both techniques were easily documented with the use of video recorders and video printers. The Sony UP-5000 color video printer produced color prints instantaneously. High-quality hard copies of the video images were obtained by both systems (Figs 4, 6, 8, 10, and 11). The ease of obtaining video recordings and color prints was equal between these two systems. However, as far as quality of image is concerned, the telescopic system provided superior documentation because of the greater depth of field.

COMMENTS

Both the Kantor-Berci and standard microscopic systems have their own merits. The advantages and disadvantages of each technique are discussed below.

Advantages of Kantor-Berci Video Microlaryngoscopic System. This system gives a magnified high-resolution image of the larynx. Excellent visualization of the anterior larynx (particularly the anterior commissure) is possible when the laryngoscope can be passed. Greater depth of field can be obtained with the use of a Hopkins telescope. No focusing is needed (when the same magnification is used during the procedure). It provides an unobstructed view of the larynx without imposing a microscope between the surgeon and the patient. Insertion of an instrument into the laryngoscope is easy. It is an excellent method of documentation and teaching. Instant color video printouts are possible.[8,9]

Disadvantages of Kantor-Berci System. The equipment is costly. The inclusive cost without a video camera is approximately $10,000 (1991), including the Karl Storz 615 xenon light source. The Supercam video camera is approximately $9,000. Insertion is not always easy because of the large size and straight outer contour of the Kantor-Berci laryngoscope. It is particularly difficult for patients with unfavorable anatomy (full set of teeth, anteriorly positioned larynx, temporomandibular joint fixation, narrow alveolar arches with deep mouth, large tongue, etc). The anterior and posterior larynx may not be visualized simultaneously in some patients, because the Kantor-Berci laryngoscope is designed to show the anterior larynx. Instrument manipulation may not be easy, particularly with a right-sided vocal cord lesion. Special instruments are needed (eg, angulated forceps, laser adapter). Focusing is necessary at different zoom magnifications when the Supercam 9050B is used. There is some image distortion due to the telescope objective lens's being located distally on the left side of the laryngoscope lumen. The operation is entirely dependent on a TV image. If the screen is small, minor lesions cannot be well appreciated. In case of a video equipment problem, surgery cannot be performed and a different system has to be employed. No pediatric Kantor-Berci video microlaryngoscope is available.

Advantages of Microlaryngoscopic System. The equipment is already available in most medical centers, including a laser adapter. The system is familiar to most surgeons. Higher magnifications can be easily and quickly obtained, producing a very sharp image at the plane of focus, allowing visualization of and operation on a minute lesion via the microscopic binocular eyepiece rather than a TV screen. Surgery thus may be performed more precisely and confidently. Microlaryngoscopes are available for both pediatric and adult patients. Televised microlaryngoscopy is an excellent method of teaching. Instant color video printouts can be obtained for documentation and the patient's record.

Disadvantages of Microlaryngoscopic System. It provides a shallower depth of field. The microscope is placed between the surgeon and the patient, making instrumentation more difficult. A light-sensitive miniature video camera and light source are needed. The operation may have to be done through one eyepiece because of the small proximal opening of the Dedo laryngoscope. With a change in magnification, refocusing is necessary.

The Kantor-Berci system produces a clear, sharp image of the larynx by using an entirely new video microlaryngoscope with a built-in Hopkins telescope, a bright xenon light source, a highly sensitive CCD camera, and a large high-resolution monitor. The microscopic system generally uses a standard light source for a microscope and a laryngoscope. To obtain high-quality laryngeal images with the microscopic system, we suggest the use of the Dedo (or Ossoff) laser video microlaryngoscope with two large light carriers, a bright light source for the microscope (even an extra supplemental illuminator such as the Benjamin-Havas clip), and a sensitive miniature CCD camera or a three-tube or three-chip video camera (Hitachi DK5050 or Sony three-chip CCD DXC 750).

One should realize that with the Kantor-Berci system, microsurgery cannot be performed without a video camera, while with the microscopic system, microlaryngoscopy can still be accomplished even though a video system malfunctions.

For both telescopic and microscopic techniques, we recommend the use of a newer color video printer such as the Sony UP-5000. With these newer color video printers, instantaneous superior-quality documentation is possible (Figs 4, 6, 8, and 10). With the Sony UP color video printers, the images obtained by color video printouts are often much better than those shown on the monitor screen.

The problems we encountered with the Kantor-Berci video microlaryngoscope were mainly related to 1) the contour and large size of the laryngoscope, resulting in insertion difficulty, and 2) the position of the telescope, resulting in some distortion and visualization problems. Our insertion failure might have been due to the fact that we happened to have a series of patients with unfavorable oral anatomy. However, we felt that laryngoscope insertion could be made much easier if the video microlaryngoscope had an hourglass shape in its middle portion.

With further refinement of the present Kantor-Berci video microlaryngoscope and with the addition of a pediatric video microlaryngoscope, the Kantor-Berci telescopic system will, in our opinion, receive a much wider acceptance by laryngologists.

SUMMARY

The Kantor-Berci system provides superior visualization of the anterior larynx with an exceptional depth of field. It is a most effective method of documentation of microsurgery of the larynx. The microscopic technique has the advantage of visualization and documentation at various magnifications, allowing a precise diagnosis and surgical procedure. The microscopic system provides much better depth of field than generally expected. In spite of the many advantages of the new Kantor-Berci system, the time-tested standard microscopic technique will remain a valuable technique in microlaryngeal surgery.

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LOWER COMPLICATION RATES ASSOCIATED WITH BRONCHIAL FOREIGN BODIES OVER THE LAST 20 YEARS

ANDREW F. INGLIS, JR, MD
SEATTLE, WASHINGTON

DAVID V. WAGNER, MD
KANSAS CITY, KANSAS

A retrospective comparison of all endoscopic bronchial foreign body (BFB) removals performed at Children's Hospital and Medical Center, Seattle, Washington, during two separate 5-year periods is reported. There were 54 patients between July 1, 1964, and June 30, 1969, and 119 patients between July 1, 1984, and June 30, 1989. Bronchoscopic removal of foreign bodies in the late cohort was performed almost exclusively with Hopkins telescope-guided foreign body graspers as opposed to traditional forceps guided by the naked eye in the first group. There were no differences in the average age, foreign body type, anesthetic technique, operative length, or anatomic distribution between cohorts. There were significantly fewer complications in the late cohort than the early. Complication rates increased with the duration of the BFB in situ. There were significantly fewer missed BFBs at initial bronchoscopy in the late cohort (4) than the early (10). Inability to endoscopically remove the BFB resulted in thoracotomy in 3 patients in the early cohort and 1 patient in the late cohort. There was one instance in which foreign body migration from right to left main stem occurred during the delay between diagnosis and operation, resulting in the necessity for emergent bronchoscopy with the patient in extremis. Prompt endoscopy in patients with suspected BFBs using the Hopkins rod bronchoscopic system will result in fewer complications and fewer missed foreign bodies.

KEY WORDS — bronchoscopy, complications, foreign bodies.

INTRODUCTION

The diagnosis and management of foreign body aspiration is extremely important. Missed or delayed diagnosis can result in respiratory difficulties ranging from chronic wheezing or recurrent pneumonias to life-threatening airway obstruction or lung abscess. The annual incidence of death from foreign body aspiration has been estimated to be between 500 and 2,000 in the United States,[1,2] and there is no evidence that the incidence of aspirations is declining.[3] A significant advance in bronchoscopy was the introduction of the Hopkins telescope in 1976 and telescope-guided forceps subsequently.[3] Because acquisition and maintenance of these instruments requires a significant commitment from the hospital operating room, this study was undertaken to assess the impact these instruments and other clinical trends in the management of foreign bodies may have on clinical outcomes.

MATERIALS AND METHODS

A retrospective chart review of all cases of foreign body aspiration treated at Children's Hospital and Medical Center, Seattle, Washington, during two separate 5-year periods is reported; a total of 173 patients undergoing treatment for bronchial foreign body (BFB) aspiration were reviewed. The early cohort consisted of 54 patients between July 1, 1964, and June 30, 1969, and the late cohort consisted of 119 patients between July 1, 1984, and June 30, 1989. Each chart was reviewed and patient characteristics, clinical presentation, time to diagnosis, techniques for removal, type of BFB found, length

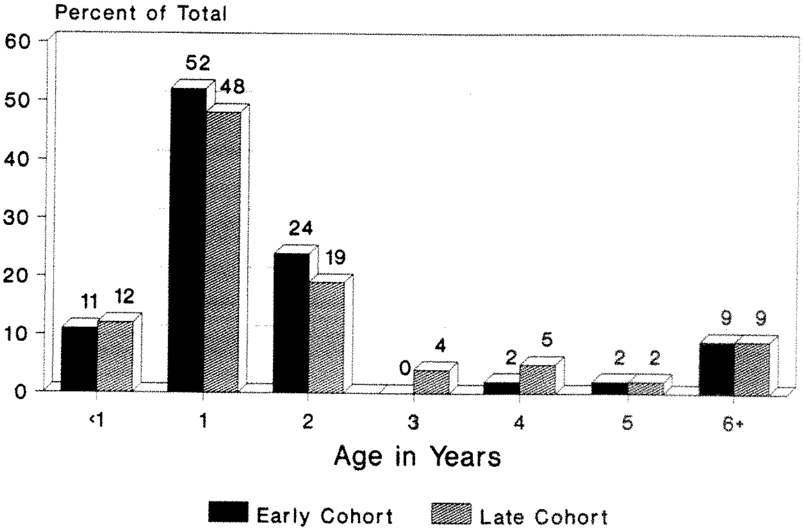

Fig 1. Age distribution of patients in early and late cohorts.

From the Department of Otolaryngology-Head and Neck Surgery, University of Washington, and the Division of Otolaryngology-Head and Neck Surgery, Children's Hospital and Medical Center, Seattle, Washington (Inglis), and the Department of Otolaryngology-Head and Neck Surgery, Kansas University, Kansas City, Kansas (Wagner).

Presented at the meeting of the American Broncho-Esophagological Association, Waikoloa, Hawaii, May 5-6, 1991.

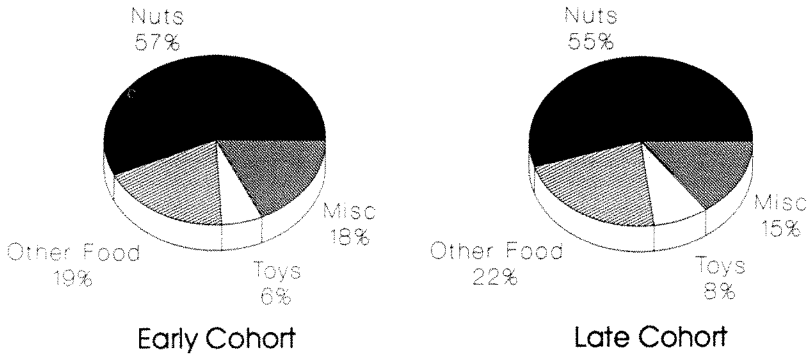

Fig 2. Types of bronchial foreign bodies encountered. Misc — miscellaneous.

of operation and hospital stay, surgeon, and complications were noted. Laryngotracheal foreign bodies were excluded.

RESULTS

Age. The patient age distribution was comparable in both cohorts. The average age was 32 months in both cohorts and median ages were 21 and 20 months for the early and late cohorts, respectively. Ages ranged from 6 months to 16 years in the early cohort and 6 months to 14 years in the late cohort. Age distribution is shown in Fig 1. Most patients were between 12 and 24 months of age.

Sex. The male to female distribution was consistent between cohorts. There were 71% boys in the early cohort and 73% boys in the late cohort.

Foreign Body Type. The BFBs were grouped into three categories: food, toys, and other. Food totaled 77% of foreign bodies in both cohorts. Nuts made up 57% and 55% of BFBs in early and late cohorts, respectively. Raw carrot fragments and popcorn kernels were also common. Toys made up 6% of the early cohort and 8% of the late cohort. Repeatedly encountered toys in the late cohort included three patients with crayon fragments and four with Lite Brite pegs. The breakdown is diagramed in Fig 2.

Clinical Presentation. A spectrum of respiratory distress ranging from none to severe with cyanosis was observed. The classic symptom triad of cough, wheezing, and unilaterally diminished breath sounds was present in nearly 65%. Three patients, less than 2%, presented in acute respiratory distress. One had bilateral BFBs and two appeared to have laryngotracheal foreign bodies that migrated to the bronchi.

We recorded the time period between BFB aspiration and treatment. In cases with no witnessed episode of aspiration an estimate was made. The distribution was virtually identical between cohorts, as shown in Fig 3. Forty-nine percent of patients received diagnoses within 24 hours. Diagnosis was made between 1 and 30 days after the onset of symptoms in 42%. Eleven percent did not receive diagnoses within 30 days of the presumed aspiration. One child suffered pulmonary symptoms for 2 years prior to bronchoscopy.

Interval Between Time of Diagnosis and Bronchoscopy. Estimates of the time interval between diagnosis and bronchoscopy were made. The average delay between diagnosis and bronchoscopy was under 9 hours in both cohorts. There was one clear-cut episode of precipitous deterioration of a patient's

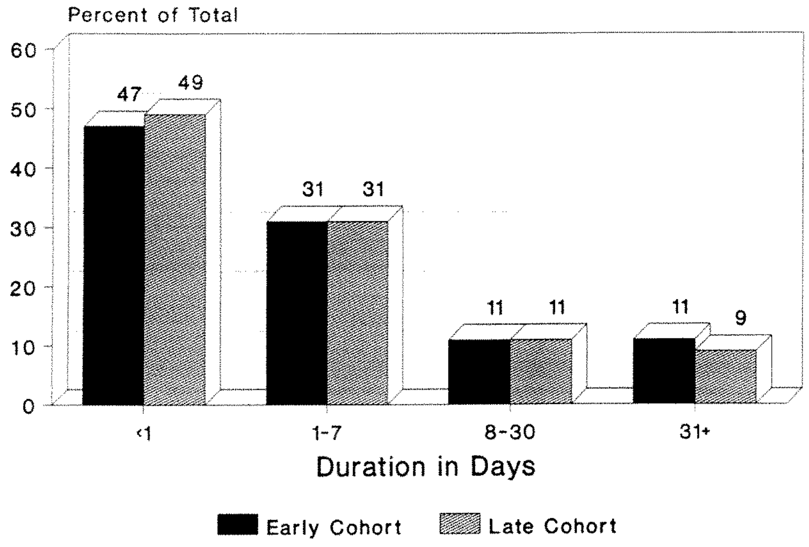

Fig 3. Time from aspiration to diagnosis.

COMPLICATIONS AND THEIR RELATIONSHIP TO INITIAL BRONCHOSCOPY AT CHILDREN'S HOSPITAL AND MEDICAL CENTER

Complication	*Present Preop* *No.*	*%*	*Arising Intraop or Postop* *No.*	*%*	*Total* *No.*	*%*
Atelectasis, persistent wheezing, or subglottic edema						
Early cohort	3	6	6	11	9	17
Late cohort	5	4	3	3	8	7
Pneumonia						
Early cohort	5	9	1	2	6	11
Late cohort	5	4	0	0	5	4
Dental injury						
Late cohort			1	1	1	1
Pneumomediastinum						
Late cohort	1	1			1	1
Pneumothorax						
Early cohort			1	2	1	2
Late cohort	2	2			2	2
Missed BFBs*						
Early cohort	5	9	5	9	10†	18
Late cohort	2	2	2	2	4†	3
Prior tracheotomy performed to secure airway						
Late cohort	1	1			1	1
Pulmonary lobectomies for incomplete BFB removal and/or pulmonary abscess						
Early cohort			3	6	3	6
Late cohort			1	1	1	1
Major complications						
Early cohort	2	4	3	6	5	9
Late cohort	2	2	1	1	3	3
Total patients with complications						
Early cohort	14	26	10†	19	24†	44
Late cohort	13	11	5†	4	18†	15

Preop — preoperatively, Intraop — intraoperatively, Postop — postoperatively, BFB — bronchial foreign body.

*Preop column shows patients with initial bronchoscopy performed outside this hospital; Intraop and Postop columns show patients with initial bronchoscopy performed at this hospital.

†$p<.05$ (χ^2).

respiratory status during the delay between diagnosis and bronchoscopy, leading to an emergent yet uncomplicated bronchoscopic removal. Findings in this case included a proximal right main stem nut fragment, a ring of mucosal edema in the proximal left main stem, and a distal left main stem nut fragment. Clinical and endoscopic findings suggested that a nut fragment in the left main stem migrated to the right main stem, leading to severe ventilatory compromise.

Anesthetic. Ninety-eight percent of the bronchoscopies were performed with an inhaled halothane anesthetic technique. Intraoperative arrhythmias occasionally forced a change to isoflurane. The remaining 2% were performed with a relaxant technique. Standard cardiopulmonary monitoring was used in the early cohort; this plus end-tidal carbon dioxide and pulse oximetry were monitored in the late cohort.

Length of Operation. The average length of operation was 26 minutes in both cohorts, ranging from 5 to 120 minutes in the early cohort and 3 to 9 minutes in the late cohort.

Location of Foreign Body. The distribution of BFBs within the tracheobronchial tree was similar in both cohorts. Thirty-three percent were in the right main stem of early cohort patients, versus 39% in the late cohort. Figures for the left main stem are 33% and 34%, respectively. The rest were in lobar or segmental branches. Multiple BFBs were present in 18% of the early cohort and 19% of the late.

Equipment. The early cohort patients were operated on with Pilling rigid bronchoscopes with distal lighting and traditional foreign body forceps. The late cohort patients were operated on with the Karl Storz pediatric bronchoscopes with visualization enhanced by the Hopkins telescope system. In the majority of cases BFBs were removed by using either the telescope-guided foreign body forceps or a Fogarty catheter and a bronchoscopic telescope.

Length of Hospitalization. Total hospitalization of less than 48 hours took place in 70% of the early cohort patients and 90% of the late cohort patients. Hospitalization for more than 24 hours for wheezing or pneumonias with undiagnosed BFBs occurred in 7% (longest, 13 days) of the early cohort and in 2% (longest, 4 days) of the late cohort. Postoperative hospitalization for longer than 2 days occurred in 26% (longest, 33 days) of the early cohort and in 6% (longest, 13 days) of the late cohort.

Operator Experience. In the early cohort, 29 of 54 bronchoscopies (54%) were performed by a single surgeon. The remaining 25 patients were distributed among 10 surgeons. In the late cohort, 58 patients and 30 patients, respectively, were treated by 1 of 2 surgeons (74%) and the remaining 31 patients were distributed among 15 surgeons. In both cohorts the majority of surgeons performed no more than 2 BFB removals in the period studied.

Complications. There were no deaths in either cohort. Complications were defined as conditions or actions leading to ongoing morbidity in the patient during the period following bronchoscopy. These included preoperative disorders requiring continued postoperative inpatient treatment as well as disorders arising during bronchoscopy or postoperatively. Complications were categorized as major or minor. Major complications were defined as those requiring more than 1 week of hospitalization postoperatively or open surgery for treatment. In-

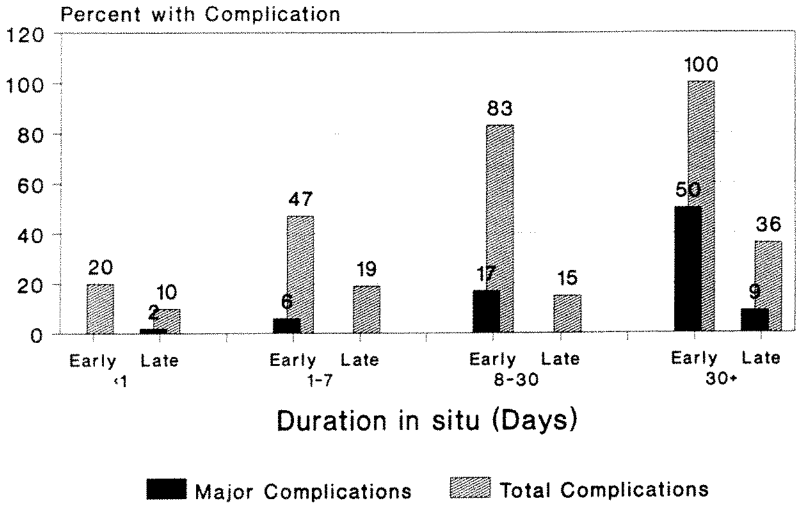

Fig 4. Complication rate versus duration of bronchial foreign bodies in situ.

traoperative anesthetic difficulties or complications were not included in the following tabulations unless they led to ongoing postoperative morbidity. Determining the nature and seriousness of intraoperative anesthetic difficulties was impossible because of a lack of uniform anesthetic record-keeping and a wide variation in the types of intraoperative monitoring used both within and between groups.

Postoperative atelectasis, wheezing, and stridor from subglottic trauma that required postoperative hospitalization for more than 24 hours were considered minor complications even if no further morbidity resulted.

Complications and their relationship to initial bronchoscopy at Children's Hospital and Medical Center for the two cohorts are listed in the Table. The complications of atelectasis, persistent wheezing, and stridor from subglottic trauma are listed together because these conditions were frequently indistinguishable on the basis of the information in the record. Overall, 44% of the patients in the early cohort had complications; 22% had complications not evident preoperatively. This was reduced to an overall rate of 15% and an intraoperative and postoperative rate of 4% in the late cohort. These reductions in complication rates were statistically significant ($p<.05$, χ^2 test). The major complication rate was 9% in the early cohort and 3% in the late cohort.

Of special note is the marked reduction in missed or incompletely removed BFBs, both from within our institution and referred from without. This difference is highly significant ($p<.05$, χ^2 test).

Complication rate versus time between aspiration and diagnosis for the two cohorts is listed in Fig 4. A clear trend for increasing complications with increasing duration of the BFB in situ was seen. It is also apparent that in every category except one, complications in the later cohort were lower than in the early cohort.

Complication rate versus operator experience was also examined. Surgeons performing two or more bronchoscopies for BFBs per year were compared with those performing fewer. For the early cohort the overall complication rate for the "more experienced" surgeons was 37% versus 52% for the "less experienced." The major complication rate was 7% versus 12% ("more" versus "less"). Corresponding figures for the late cohort were an overall complication rate of 13% (more experienced) versus 23% (less experienced) and a major complication rate of 2% (more) versus 0% (less). None of these differences were statistically significant.

DISCUSSION

The goals of this study were to examine the safety of bronchoscopy for BFB removal in a historical context by looking for clinical trends and any impact provided by the improved visualization from Hopkins telescopes. Several conclusions can be drawn.

Our two study populations were strikingly similar in terms of sex, age, and types of foreign bodies aspirated. The similar makeup of both cohorts allows comparisons.

The 70% male preponderance appears to be one of the fixed mathematical constants of nature (like Planck's constant or the speed of light) and has been observed in other series.[1-5] It has been attributed to rougher and more adventurous play in male infants.[2,3,5-7]

The age distribution, with the majority of patients between 9 and 24 months, is also consistent with those of other series and has been attributed to poor chewing ability from a lack of posterior dentition,[2,5,6] a tendency to put things into the mouth,[2,4,6] and a tendency to have frequent, vigorous, uninhibited inspirations when startled, laughing, or crying.[7]

There was also marked consistency in the type of

BFBs over the 20 years studied, and in the percentage of patients described as having multiple BFBs. It is interesting to note that the percentage of toys aspirated would have decreased instead of increased had the late cohort not had access to Lite Brite pegs.

The greater number of patients in our later cohort probably reflects the increase in population in the Seattle area over the 20-year study period.

This review shows clearly the relationship of increasing complication rates with increasing time to diagnosis. Early diagnosis and treatment is vital. Unfortunately, there has been no trend for earlier diagnosis, as shown in Fig 3. Early treatment is hindered by the close resemblance of the symptoms of a BFB to those of the much more common problems of asthma and bronchiolitis, and to a lesser extent by the preference for a trial of conservative management of BFBs by some physicians in our community. There is a clear need for ongoing education to increase the index of suspicion and the ability to make appropriate management decisions.

Perhaps surprisingly, there was no decrease in the operative time in the late cohort. While it appears the Hopkins telescope allows more thorough airway evaluation and more complete BFB removal, it does not make the process quicker.

The trend for decreased numbers of patients preoperatively hospitalized with undiagnosed BFBs is probably secondary to the improved diagnostic sophistication of the staff of our tertiary care center.

The trend for shortened postoperative hospitalization is mainly secondary to fewer BFBs being missed (allowing prompt resolution of symptoms) and the lower complication rate overall.

The overall complication rate fell for a number of reasons. The improvement most clearly attributable to the Hopkins telescope is the decreased incidence of missed or incomplete BFB removal. The improved visualization afforded by the telescopes and the improved "reach" provided by Fogarty catheters and the miniature flexible alligator forceps resulted in fewer repeat bronchoscopies and thoracotomies. This represents a significant advance.

The drop in patients hospitalized postoperatively for observation of pulmonary problems such as pneumonia, atelectasis, wheezing, and subglottic trauma is probably secondary to an increased confidence in outpatient management. Further, subglottic trauma may have been lessened because the visualization afforded by telescopes allows for the use of more age-appropriate (ie, smaller) bronchoscopes.

There was not a statistically significant difference in complication rates associated with the experience of the surgeon. The higher major complication rate associated with the "more experienced" surgeons in the late cohort is secondary to referral patterns in our institution that send the most difficult cases to the most experienced bronchoscopist available. Two of the three major complications in this cohort occurred prior to bronchoscopy.

Once the decision to perform bronchoscopy has been made, the question arises as to the safety in waiting 1) for the nothing-by-mouth status to be cleared and 2) until regular operating hours the next morning if the diagnosis is made late at night. In reviewing our 173 cases here, there was only one episode in which a delay resulted in a serious deterioration of the patient's condition. It should be kept in mind that 1) there may have been other patients whose deteriorating condition was not well documented on the record, and 2) most patients who presented acutely were operated on acutely. It is our recommendation to perform bronchoscopy 1) urgently on all patients having respiratory distress, 2) soon after the nothing-by-mouth status is safe in patients who present acutely following aspiration but are having no distress, and 3) within a reasonable time in the patient with long-standing pulmonary symptoms in whom a BFB is suspected.

One frustration associated with this study was our inability to determine the outcomes associated with different techniques of anesthetic administration and monitoring. The events leading up to, the magnitude of, and the morbidity associated with episodes of hypoventilation, hypoxemia, cardiac arrhythmias, hypotension, etc, were not easily gleaned from the record. The impact on safety of pulse oximetry is also unknown. A prospective study is needed.

CONCLUSIONS

1. There has been no significant change in patient age distribution, the types of BFBs, and the anatomic distribution of BFBs in the tracheobronchial tree in the last 20 years.

2. There has been no improvement in the rapidity of diagnosis of BFBs in the last 20 years, and rapid diagnosis is associated with better outcome.

3. Removal of BFBs can be efficiently performed without the use of bronchoscopic telescopes, but the use of telescopes results in significantly fewer missed and incompletely removed BFBs, thus offering a major advantage.

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FIRST INTERNATIONAL SKULL BASE CONGRESS

The First International Skull Base Congress will be held June 14-20, 1992, in Hanover, Germany. For further information, contact Madjid Samii, MD, Professor and Chairman of Neurosurgery, Medical School Hanover, Neurosurgical Clinic, Hospital Nordstadt, Haltenhoffstr 41, D-3000 Hanover 1, Germany; phone 0049-(0)511-7638245 or 623151, FAX 0049-(0)511-7638606.

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AESTHETIC SURGERY OF THE FACE

A symposium on Aesthetic Surgery of the Face will be held March 26-28, 1992, in San Francisco, California. This meeting is sponsored by the Division of Plastic Surgery, University of California, San Francisco, and Davies Medical Center. For further information, contact Ashley Carpenter, Extended Programs in Medical Education, Room LS-105, USCF, San Francisco, CA 94143; (415) 476-4251.

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MULTICHANNEL ELECTROMYOGRAPHIC OBSERVATIONS IN SPASMODIC DYSPHONIA PATIENTS AND NORMAL CONTROL SUBJECTS

STEVEN D. SCHAEFER, MD
DALLAS, TEXAS

RICK M. ROARK, PHD
DALLAS, TEXAS

BEN C. WATSON, PHD
DALLAS, TEXAS

GEORGE V. KONDRASKE, PHD
ARLINGTON, TEXAS

FRANCES J. FREEMAN, PHD
DALLAS, TEXAS

ROBERT W. BUTSCH, MS
DALLAS, TEXAS

JOHN POHL
ARLINGTON, TEXAS

Spasmodic dysphonia is primarily a disorder of vocalization. Increasing evidence, however, suggests that individuals with this disorder comprise a heterogeneous population characterized by abnormal motor control throughout the vocal tract. Multichannel simultaneous electromyography was performed on 11 spasmodic dysphonia patients and 10 normal awake subjects to investigate both the distribution of neuromotor abnormality within the vocal tract (eg, intrinsic and extrinsic laryngeal muscles, tongue, and palate) and the contribution of activation of higher central nervous system centers to observed abnormality. Experimental tasks ranged from vegetative (quiet breathing) to simple linguistic (short sentences). Digitized electromyographic signals were analyzed to compute the amplitude envelope and extract a set of parameters that represent amplitude characteristics. Electrode insertions were cross-validated by quantitative analysis of patterns of activation across selected reference tasks and by traditional qualitative methods. Between-group differences were found for measures of normalized median and peak token amplitudes. These differences are both task- and measure-dependent. Results highlight the complex and interactive effects of muscle, task, and quantitative measures on between-group differences.

KEY WORDS — multichannel electromyography, spasmodic dysphonia, voice.

INTRODUCTION

The initial description of spasmodic dysphonia (SD) as a form of nervous hoarseness by Traube[1] initiated the view, widely held over the subsequent century, that SD was solely a functional disorder. Elaborate statements endorsing this view were made based on the bizarre presentation of SD patients. Any consideration that such patients, or a subset of these patients, might have an organic disorder was dismissed.[2] In contrast, work beginning with Aronson et al[3,4] suggested the findings of voice tremor, facial or tongue twitches, and head or neck tremor were highly linked neurologic signs rather than incidental findings in a presumed psychiatric population. Additional evidence of an organic substrate to SD has come from various investigations showing auditory brain stem, gastric acid secretory (visceral vagal efferents), electromyography (EMG), blink reflex, and structural and functional brain abnormalities in part of the SD population.[5-11] Given this body of evidence, we believe that direct measures of human vocal tract neuromotor activity should further our understanding of SD, and perhaps our understanding of central nervous system (CNS) motor control of the vocal tract.

One approach to broadening our understanding of SD is to apply EMG measures to examine the nature and extent of vocal tract deficits in affected subjects. Such an approach must be recognized as having several inherent problems due to the population under study and the complexity of acquiring and analyzing multichannel vocal tract EMG. In regard to problems in studying a population of SD subjects, the first consideration is the heterogeneity of individuals who often share only their pattern of abnormal voicing. Some subjects may have several coexistent neurologic findings indicative of an organic basis for their disorder, while others remain a diagnostic challenge. Blitzer et al[12] have further characterized SD as a form of either focal (involving only the larynx) or generalized dystonia. Obviously, any one EMG measure of such a heterogeneous population could be expected to vary from subject to subject. However, a pattern of abnormalities may emerge from analysis of multiple EMG measures across muscles, tasks, and subjects.[12-15] A second consideration in studying SD by EMG is the observation that spasticity is exacerbated by increasing the communicative intent of the task.[13] For example, a pattern of essentially normal vocalization for static or sustained tasks, such as the vowel /i/, followed by impaired vocalization during simple sentences is one of the characteristics of SD thought to

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From the Department of Otolaryngology (Schaefer, Roark, Butsch), University of Texas Southwestern Medical Center, Dallas, Callier Center for Communicative Disorders, University of Texas at Dallas (Watson, Freeman), and Human Performance Institute, University of Texas at Arlington (Kondraske, Pohl), Texas. Supported by National Institutes of Health grant R01-DC 00410-03.

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REPRINTS — Steven D. Schaefer, MD, Dept of Otolaryngology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75235-9035.

be consistent with a psychiatric disorder.[16] Such a behavior within the same subject confounds testing confined to one or two speech tasks, since this approach fails to consider the well-recognized performance variability. This variability may reflect activation of hierarchically organized centers for vocal motor control within the CNS. A third consideration is the effect of the testing procedure on the patient's behavior; that is, results are influenced by the structure of vocal tasks, the testing environment, the interaction of the subject with investigators, subject instructions, and subject compensatory behaviors.[16]

In regard to vocal tract EMG, there are several additional considerations. First, the human vocal tract is best viewed as a highly integrated, dynamic, and adaptive system extending from the diaphragm to the lips. Experimental paradigms must provide for simultaneous measures of multiple elements of this system within the constraints inherent in human testing. With a few important exceptions,[17-20] vocal tract EMG has been limited primarily to concentric needle electrodes within a few endolaryngeal muscles during performance of static vocal tasks. A second consideration is the distinction between normal and pathologic performance on multiple simultaneous EMG measures of the human vocal tract. For example, a particular muscle might have a "normal" pattern of neuromotor activity as measured by the quality or quantity of electrical activity, but be inappropriately activated for a given vocal task. Third, descriptions of EMG abnormalities have often been qualitative. Given the unique function and anatomy of the vocal tract and the characteristics of laryngeal muscles, such analyses may be inadequate to describe the extent of abnormality in SD.[15,21] However, techniques for quantification and statistical comparisons can build upon EMG studies of the extremities.[22]

In an attempt to address many of the above problems, we evaluated SD patients and normal control subjects using a series of acoustic, kinematic, aerodynamic, and EMG measures. This report focuses on our initial quantitative evaluation of a subset of these data. Group comparisons are made for simultaneous EMG findings from vagally and nonvagally innervated muscles and clinical-perceptual findings of the study population performing tasks at points along a hierarchy of increasing linguistic and motoric complexity.

METHOD

Subjects. Eleven SD patients and 10 control subjects underwent simultaneous acoustic, kinematic, and EMG recordings in compliance with the informed consent policies of the Institutional Review Board of the University of Texas Southwestern Medical Center. The SD subjects included 4 men and 7 women (average age 48.6 years, range 25 to 69 years) who were drawn from a larger population of subjects who participated in extensive otolaryngologic and neurologic examinations, as well as static and dynamic brain imaging. Diagnosis of SD was made by a minimum of two otolaryngologists and two speech-language pathologists using both perceptual and fiberoptic laryngoscopic (ie, hyperadduction of vocal folds) criteria. No subject had structural or other laryngeal abnormalities that might confound measures employed in this study. Causes of SD were thought to be cerebral microvascular disease in 2 patients and familial in 1 patient, and were unknown in 8 patients. Duration of dysphonia varied from 1.5 to 20 years (average 8.6 years).

Ten control subjects, consisting of 4 men and 6 women (average age 42.1 years, range 25 to 51 years), were recruited from normal volunteers. Controls were matched as much as possible for gender and age of the study population. None of these subjects had a history of speech or neurologic disorders. History and physical findings were unremarkable and these control subjects were regarded as healthy examples of their respective age groups.

Muscle Selection, Electrode Insertion, and Verification. Recordings were made over two sessions (sessions 3 and 4) in awake, nonsedated subjects in the Vocal Tract Physiology Laboratory (an electrically shielded room) at the University of Texas Southwestern Medical Center. The same personnel participated in all sessions. These sessions were designed to measure multiple parameters of the human vocal tract, and for the purpose of this report, discussion is limited to acoustic and perceptual data and EMG findings in the left levator palatini (LP), genioglossus posterior (GGP), and right thyrohyoid (THD) muscles and both thyroarytenoid (TA) muscles. These muscles were selected to give a range of findings in vocal tract sites innervated by the vagus and hypoglossus nerves.

Bipolar hooked-wire electrodes were constructed using 0.05-mm coated platinum wire (Semiconductor Packaging Materials Inc; effective recording area 1 mm) and were inserted perorally (LP muscle) or transcutaneously.[23] Anesthesia was limited to 1% lidocaine hydrochloride intradermally or 4% lidocaine hydrochloride on mucosal surfaces at electrode insertion sites. Subjects were awake, unsedated, and withdrawn from any medication that might confound findings for a minimum of 2 weeks. Output from each electrode pair was routed to separate EMG amplifiers (Grass Instrument 7P511) through a shielded cable. Amplifiers were carefully calibrated and maintained to ensure accuracy of signals and to minimize extraneous noise. The impedance at each input terminal of the preamplifiers was ≥ 20 MΩ. Sensitivity varied from 5 to 75 μV/mm depending on the electrode configuration and muscle. Each channel was band-pass-filtered

TABLE 1. TASKS UNDER ANALYSIS

Type of Task	*Task*
Reference and verification	Tongue protrusion
	Swallow
	Valsalva maneuver
	High-pitched /i/
	Sustained "sh"
Vegetative	Quiet oral breathing
Paralinguistic	Sustained modal /i/
	Sustained modal /m/
Linguistic	*beep, beep, beep, beep, beep*
	beep, beep went the heap

Lists only those tasks being analyzed for this report and is drawn from protocol of 48 tasks performed over two sessions. Tasks might serve as both reference or verification and paralinguistic tasks (eg, sustained "sh").

with half amplitude points at 30 Hz and 3,000 Hz. A notch filter was used to minimize 60-Hz interference. All EMG signals were evaluated before and during recordings for extraneous artifacts by using a Tektronix model 11401 digital oscilloscope. Signals from the amplifiers were recorded on analog tape by using a 14-channel FM tape recorder (TEAC-XR-510). Nominal full scale signal amplitudes were ±2 V peak. Recording bandwidths were 2.5 kHz for frequency modulation (FM)–coded EMG channels and 18 kHz for the acoustic direct channel. Verification of insertions followed procedures developed at Haskins Laboratories and was based on appropriateness of electrical activity for a given muscle during specific maneuvers.[17-19] Such maneuvers included but were not limited to the following: 1) activation of the GGP muscle on tongue protrusion and swallowing, 2) activation of the THD muscle on swallowing and neck flexion, 3) activation of the LP muscle on voiceless fricative sounds and swallowing, and 4) activation of the TA muscle on the Valsalva maneuver, swallow, and phonation, but not on inspiration.

Experimental Paradigms and Data Acquisition. All subjects were familiar with the basic experimental tasks and conduct of the testing procedures, having undergone two prior 2- to 3-hour sessions dealing primarily with multiple kinematic, acoustic, and aerodynamic measures of vocal tract function. Subjects were seated in a standard otolaryngologic examination chair with the head fixed 20 cm from an Audio-technica ATM33R electric condenser microphone mounted to the chair. All experimental sessions were cued by a visual pacing light controlled by a desk top computer (Compaq 386/25) operating under the in-house–developed software program ACQUIRE.[24] Experimental tasks were randomly presented by the computer. Each task was guided by the computer-controlled pacing light in a highly reproducible and standardized fashion. Three to five repetitions or tokens of each vegetative, paralinguistic, and linguistic task were performed. For the purpose of this report, analysis is limited to tasks selected from a protocol of 48 (Table 1). Rank-ordered from lowest to highest complexity, these tasks are 1) quiet tidal oral breathing, 2) middle-pitch /i/ (mid /i/), 3) *beep, beep, beep, beep, beep* (beep..beep), and 4) *beep, beep went the heap* (beep..heap).

ACQUIRE software facilitated quality control by operating amplifiers, FM recorders, calibration procedures, and identification of tasks and tokens. At the completion of each session, a printed copy of the performed experimental tasks was provided by the system to verify each event against a handwritten task assessment form used by the investigators.

Acoustic and Perceptual Analysis. Clinical-perceptual analyses of each token were completed by four speech-language pathologists. All four were experienced in evaluating voice characteristics of SD. Mid /i/, beep..beep, and beep..heap were evaluated for presence and severity of strain-strangle quality. Randomized tokens were presented to the evaluators, who were blinded as to the identity of specific individuals and to the pattern of randomization. Strain-strangle was rated on a scale of 0 to 7 (7 = worst).

Data Conversion and Calibration. Analog data from FM tapes were converted to digital form after the data acquisition session. The computer program CONVERT automatically controlled playback of the multichannel tape recorder, a 12-bit digitizer board (Data Translation 2821-F-16SE), and storage of data to magnetic disk media.[24] The EMG signals were low-pass-filtered prior to digitization to reduce high-frequency noise and ensure antialiasing. Constant delay sixth-order analog filters (Frequency Devices 9002) were used at −3 dB cutoff frequencies of 2,500 Hz. Sampling of EMG data occurred at 5,000 samples per second. Acoustic data were similarly filtered at 5,000 Hz and digitized at 10,000 samples per second. Quantitation error due to digitization was 0.0122%. Data files were computer coded during the acquisition and digitization sessions according to subject, session, task, token, and signal channel.

Precision calibration signals recorded during the acquisition session were likewise digitized and analyzed to obtain baseline and multiplication parameters for each signal channel. These parameters were used to convert all EMG data to absolute microvolt units, within a 5% margin of precision. Once calibrated, data were stored to write once, read many (WORM) optical media, from which they could be routinely accessed by computer-aided analysis programs.

Data Analysis. Figure 1 shows EMG and acoustic signals beep..heap for an SD subject. Raw EMG files were first screened visually for quality. Signals that contained artifact or were saturated were eliminated from the data corpus. A file representing the envelope of the signal was computed for each of the

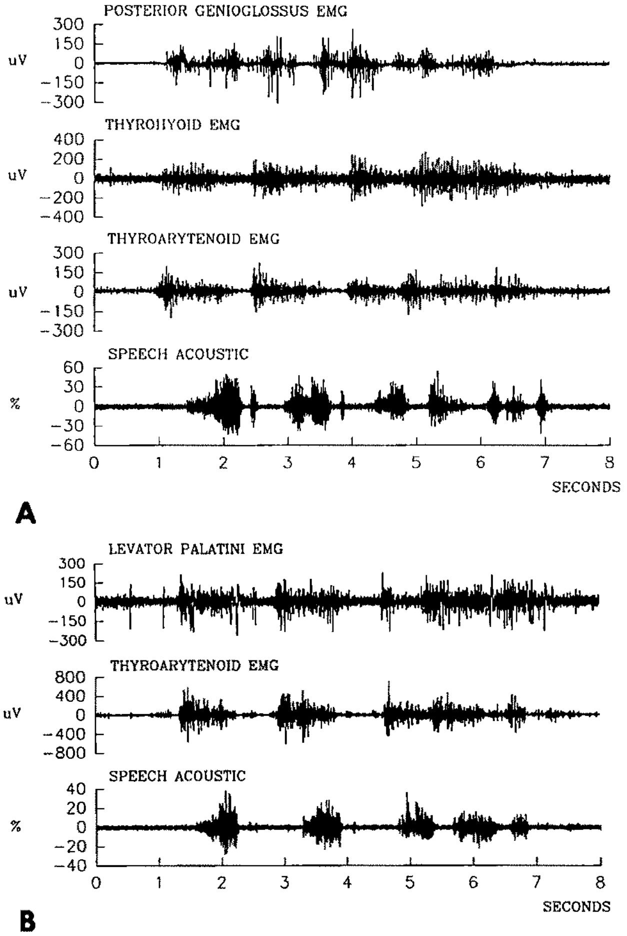

Fig 1. Multiple electromyographic (EMG) and speech acoustic signals recorded during *beep, beep went the heap* produced by the same spasmodic dysphonia subject during two of four data acquisition sessions. Electromyographic signals are calibrated to microvolts and acoustic signals are normalized to percent of maximum observed during single session. A) Session 3. B) Session 4.

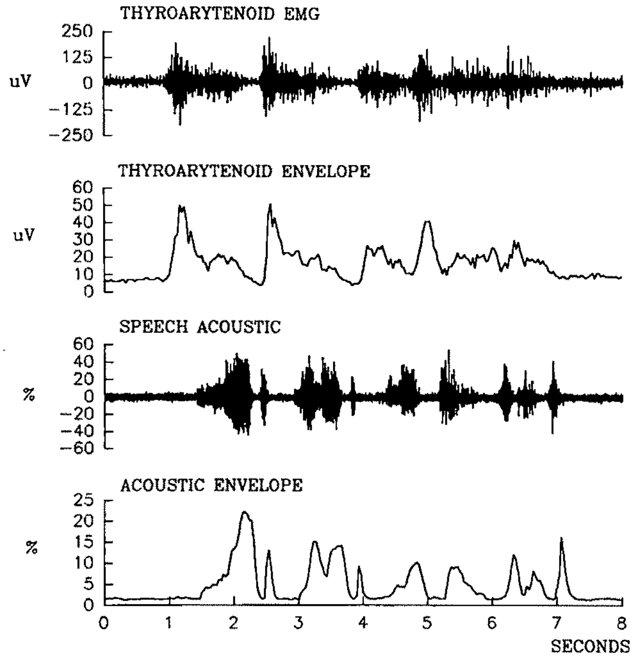

Fig 2. Thyroarytenoid electromyographic (EMG) and speech acoustic signals from Fig 1A for *beep, beep went the heap* along with their corresponding envelopes determined by computer processing. All EMG and acoustic signals are windowed to extract time interval of interest for each session task by using visual and acoustic playback methods.

remaining EMG files as well as for the acoustic signal. Generation of envelope files required several steps. First, any residual DC offset was removed by subtracting the average amplitude value from each data point. The signal was then rectified and digitally low-pass-filtered (cutoff frequency, 10 Hz). Data were then software down-sampled at an effective rate of 30 Hz for inclusion in the envelope files to reduce the size of these files (5,000:30 ratio) and therefore increase the speed of subsequent analyses. Figure 2 shows raw EMG and acoustic signals and corresponding envelope files for beep..heap for the same subject as Fig 1.

Custom software was developed to automatically process envelope files to extract selected measures. This software presented envelope files visually to allow an operator to select start and end times within a file, thereby identifying a segment for subsequent processing. Typically, the acoustic envelope was displayed first, then start and end times were selected, and these were applied to select segments from all signals recorded simultaneously and associated with that token. All signals for a given token were analyzed over the time segment selected to derive a common set of parameter measures. Parameters computed and saved were 1) start time (seconds into file), 2) end time (seconds into file), 3) peak amplitude (microvolts), 4) time into event when peak amplitude occurred (percentage of segment duration), 5) mean amplitude, 6) median amplitude, 7) percentage of event duration during which the signal was above the average amplitude, and 8) ratio of average to peak amplitude. The last two parameters were designed to capture information regarding the gross shape of envelope signals in a manner that is independent of absolute amplitude and are included as a prelude to more detailed temporal analyses. After parameter files were computed for each envelope file, intraindividual average values for each parameter were computed by averaging across values in parameter files representing different tokens of the same task. To conclude the first phase of analysis, the resulting averaged parameter files were concatenated (all parameter files for a given subject) into a single ASCII text file (one per subject) with proper delimiters included for subsequent importing to a spreadsheet. Each of the above steps was facilitated with custom analysis software.

Spreadsheet-compatible parameter files were imported to a MacIntosh computer (MAC II) using Microsoft EXCEL. This spreadsheet consisted of approximately 1,100 rows (21 subjects x 9 tasks x 6

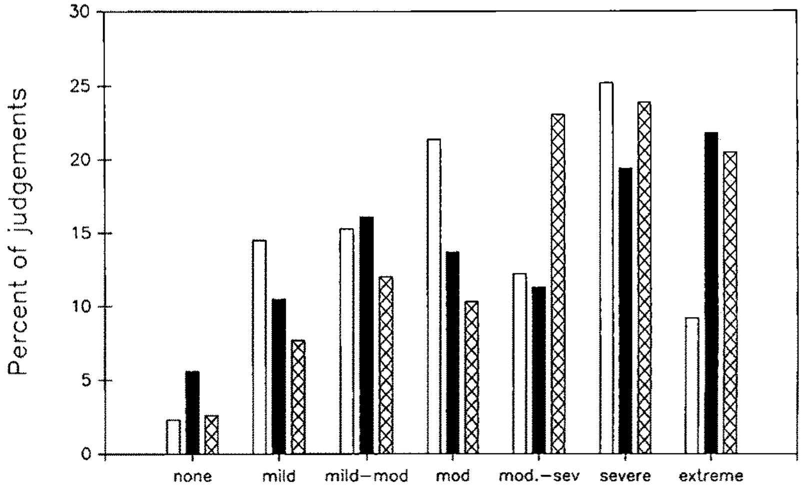

Fig 3. Perceptual judgments of severity of strain-strangle voice quality in spasmodic dysphonia subjects. Empty bars — sustained /i/; dark bars — five repetitions of *beep*; cross-hatched bars — *beep, beep went the heap*.

channels) and 22 columns (identifiers and computed parameters), or approximately 24,000 cells (a data reduction from approximately 110 megabytes of time series data). From this array, a variety of data groupings and restructuring was performed manually to support the last phase of analysis. These analyses included 1) basic descriptive statistics for raw parameters, 2) determination of which task maximally activated a given muscle, and 3) comparison of normal and SD groups as a function of task complexity.

Means and standard deviations were computed for each group separately for each task-muscle combination. Candidate reference tasks were either dynamic (eg, swallow) or sustained (eg, tongue protrusion or sustained "sh"). Peak and median amplitude measures were used to indicate level of activity for dynamic and sustained tasks, respectively. Initial analysis was performed intraindividually. Tasks were rank ordered on the basis of their relative ability to activate a given muscle for a given subject. After rankings were established for all muscles and all subjects, the percentage of observations for which task A was ranked first for a given muscle was computed. Task A was then designated the reference task for that muscle.

Establishment of reference tasks is not only a separately identified analysis, but one that is a necessary precursor to the analysis of differences between normal and SD groups as a function of task complexity. Normalized amplitude parameters were added to the parameter record for each token by dividing peak, mean, and median amplitude values for a given muscle by the activity level index (ie, median or peak amplitude value) associated with the corresponding reference task for that muscle. Thus, the respective normalized parameter represents a characteristic of muscle activity in terms of the percentage relative to reference task activation.

RESULTS

Acoustic and Perceptual Analysis. Distributions of ratings of strain-strangle quality for mid /i/, beep ..beep, and beep..heap are shown in Fig 3. Chi-square analyses revealed significant differences between mid /i/ and beep..beep ($\chi^2 = 12.43$, $p = .05$) and between /i/ and beep..heap ($\chi^2 = 17.52$, $p = .008$). The difference between beep..beep and beep ..heap was not significant.

Reference Tasks. Activity levels for verification reference tasks are shown in Table 2. Each table cell contains two entries representing the percentage of observations for which the given task produced a rank of 1 (ie, maximal activation) across all tasks analyzed. The left-side entry (denoted M) is based on computation using the median amplitude for each task, whereas the right-side entry (denoted M + P) is based on computation using the median amplitude for sustained tasks and the peak amplitude for dynamic tasks (eg, swallow). The Table has three sections representing analysis of normal, SD, and combined groups. Thus, the 70/30 entry in the first cell for normal subjects indicates that the genioglossus was maximally activated by tongue protrusion in 70% and 30% of the normal subjects using M and M + P, respectively. Peak activity during swallow was taken as the reference for normalizing EMG amplitude measures prior to within-group comparisons, since it is evident from M + P entries that swallow maximally activates all muscles on a frequent basis. To illustrate specificity of activation by task, M entries are shown graphically for the combined group in Fig 4. These values demonstrate specificity of activation of each muscle by the task selected a priori to verify electrode placement.

Group Comparisons. Several parameters were used to investigate differences between normal and SD subjects. One of these is the ratio of the envelope average amplitude to peak amplitude. This simple measure is expected to reflect gross dynamic differences. Figures 5 and 6 show coefficients of variation for normal and SD subjects associated with the average-to-peak ratio measure for the GGP and LP muscles across tasks. These findings show group dif-

TABLE 2. REFERENCE TASK ANALYSIS

Muscle	*Tongue Protrusion*	*Swallow*	*High-Pitched /i/*	*Valsalva Maneuver*	*Sustained "sh"*
Normal group					
Genioglossus	70/30	0/60	20/10	10/0	
Thyroarytenoid	0/10	0/70	38/0	63/20	
Thyrohyoid	0/10	20/80	70/10	10/0	
Levator palatini		20/75		43/13	29/13
Spastic dysphonia group					
Genioglossus	91/36	0/64	9/0	0/0	
Thyroarytenoid	9/0	0/60	9/10	82/30	
Thyrohyoid	18/9	9/82	36/0	36/9	
Levator palatini		30/91		50/9	20/0
Combined group					
Genioglossus	81/33	0/62	14/5	5/0	
Thyroarytenoid	5/5	0/65	21/5	74/25	
Thyrohyoid	10/10	14/81	52/5	24/5	
Levator palatini		29/84		47/11	24/5

Results of analysis to determine activation of muscles by candidate reference tasks. Each table cell represents percentage of observations for which given task produced rank of 1 (ie, maximal activation) across ranking sample set that included all tasks. Results are shown for rankings based on 1) median electromyographic envelope amplitude for all tasks (left-hand value), and 2) those based on median envelope amplitude for sustained tasks plus peak envelope amplitude for swallow (right-hand value).

ferences that depend on the task-muscle combination. The SD subjects showed greater variability in this measure than normals for the GGP muscle during mid /i/, but not during other tasks. In contrast, SD subjects showed greater variability than normals for the LP during the beep..beep and beep ..heap tasks, but not during other tasks.

Normalized activity parameters (peak, mean, and median amplitude) were computed by using the peak amplitude obtained during swallow for a given muscle and subject as the basis for normalization. Figure 7 contains results of this analysis for the TA muscle across tasks. Normalized peak values were used for dynamic tasks such as beep..beep, while normalized median amplitude values were used for mid /i/. A two-way ANOVA on this data set yielded a marginally significant group effect ($p \leq .06$) and a significant group-task interaction ($p \leq .020$). By using Scheffe's method to identify the source of this effect, significant group differences were found for both beep..beep and beep..heap, while differences for quiet breathing and mid /i/ were not significant. Similar analysis for the THD muscle found a significant task effect, but no group effect. The reader will recall that SD subjects showed significant increases in the perceived severity of strain-strangle voice quality for the beep..beep and beep..heap tasks. The decrement in voice quality is likely a reflection of abnormal increases in TA activity for these tasks.

DISCUSSION

The study reported herein applied quantitative measures of EMG signals to test two specific hypotheses regarding vocal tract neuromotor abnormalities in SD: 1) EMG abnormalities in SD are present in vocal tract musculature remote from the larynx, and 2) EMG abnormalities in SD increase as tasks increase in linguistic and motoric complexity. This study also examined the relation between clinical judgments of strain-strangle voice quality and TA activity in SD subjects. To achieve these ends, we reported selected quantitative measures of EMG signals recorded from an intrinsic laryngeal muscle (TA), an extrinsic laryngeal muscle (THD), and nonlaryngeal muscles (GGP, LP). Tasks selected for analysis represent points along a theoretic continuum of increasing complexity and ranged from nonspeech vegetative to simple linguistic.

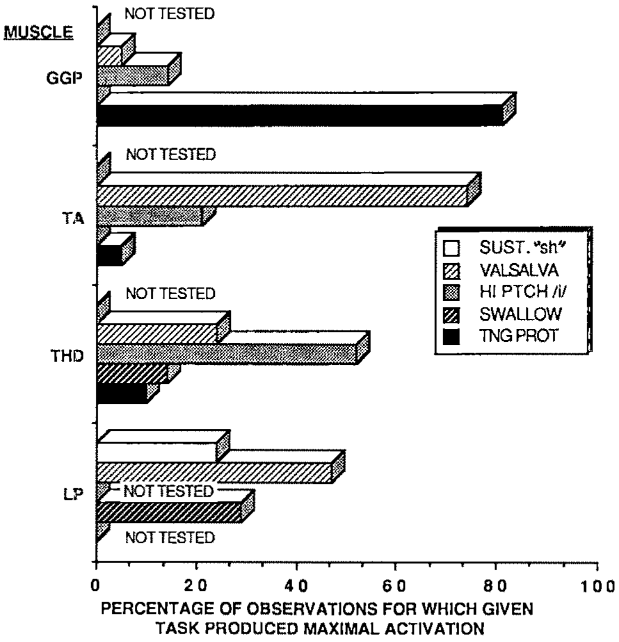

Fig 4. Muscle activation specificity during reference tasks for combined normal and spasmodic dysphonia subjects. TNG PROT — tongue protrusion, NOT TESTED — not analyzed for this graph, GGP — genioglossus posterior, TA — thyroarytenoid (both), THD — right thyrohyoid, LP — left levator palatini.

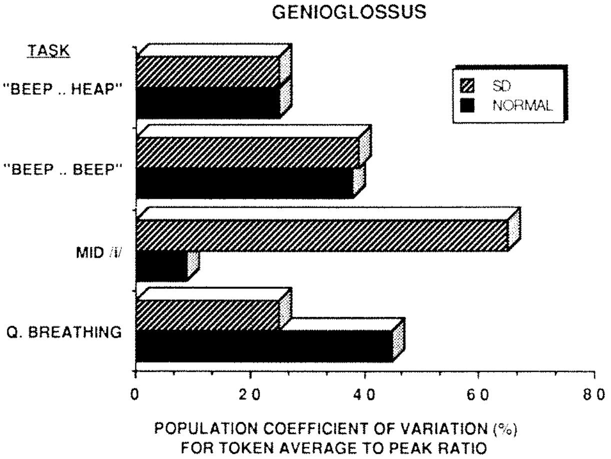

Fig 5. Comparison of normal and spasmodic dysphonia (SD) group coefficients of variation computed for average-to-peak ratio measure of genioglossus electromyographic envelopes for four tasks. Q. BREATHING — resting tidal oral breathing.

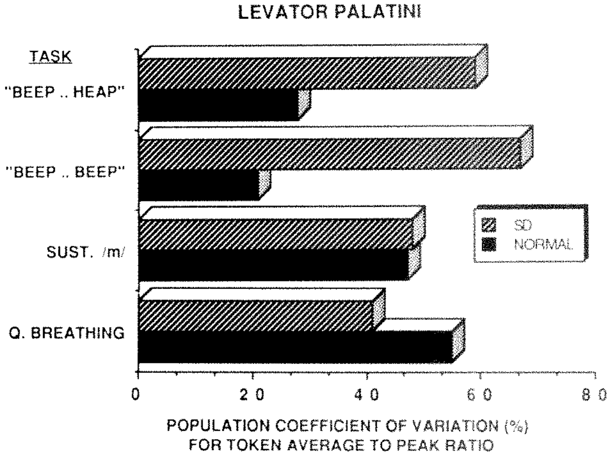

Fig 6. Comparison of normal and spasmodic dysphonia (SD) group coefficients of variation computed for average-to-peak ratio measure of levator palatini electromyographic envelopes for four tasks. Q. BREATHING — resting tidal oral breathing.

The first step in developing quantitative measures of the EMG signal was to examine the utility of these measures in verifying electrode placement and in identifying reference tasks for normalization of raw EMG signals prior to within- and between-group comparisons. Typically, EMG studies verify electrode placement by qualitative evaluation of patterns of muscle activation or inhibition during specific tasks.[18,19,23] Herein, we reported quantitative differences in median muscle activity across verification and reference tasks. This technique provides an objective approach to verification of electrode insertion.

Reference tasks for normalization of EMG signals may represent theoretic maximum or minimum activity for a given muscle. Since the experimental tasks we analyzed should elicit less than maximum activity, we sought to normalize EMG signals relative to maximum activity. With the exception of the swallow, all verification reference tasks were sustained. The inherently dynamic nature of a swallow suggests that maximum activation of a specific muscle cannot be maintained throughout the gesture. Therefore, we examined peak activity levels for each muscle during the swallow. When this measure was considered, all muscles showed maximum activity for the swallow. Thus, quantitative analyses permitted objective identification of the same reference task for all muscles. While we know of no other studies reporting vocal tract EMG that attempted to quantify electrode verification and selection of reference tasks, this strategy appears to be valid and may provide a mechanism for standardization of EMG data analysis. Such standardization will facilitate cross-study comparisons.

Between-group comparisons for the subset of tasks, muscles, and measures reported here revealed EMG abnormalities in multiple vocal tract muscles. Abnormalities were observed in muscles innervated by the vagus (TA, LP) and hypoglossus (GGP) nerves. However, these measures did not reveal abnormalities in another hypoglossus-innervated muscle (THD). In general, these findings are consistent with qualitative and quantitative abnormalities reported for a different set of SD patients by Schaefer et al.[15] Between-group comparisons also revealed differential neuromotor deficits as a function of task complexity. That is, SD subjects showed increased abnormality relative to normals as tasks increased in complexity. Post-test comparisons revealed significant between-group differences for normalized TA activity for beep..beep and beep..heap, but not for mid /i/ ($p < .05$). We have argued elsewhere that increased task complexity may represent increased participation of higher cortical and adjacent subcortical levels within the CNS.[15] The distribution of

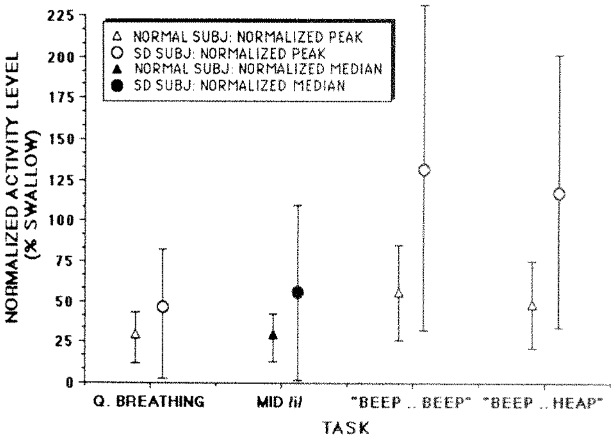

Fig 7. Comparison of normal and spasmodic dysphonia (SD) group thyroarytenoid levels across different tasks. Group means and standard deviations are shown for normalized activity level measures, obtained by dividing raw envelope amplitude characteristics (peak or median) by reference value (peak amplitude exhibited by given muscle during swallow by given subject). Normalized peak and median values are used for dynamic and sustained tasks, respectively.

neuromotor abnormalities within the vocal tract and the finding of increased abnormality with increased task complexity in these SD subjects are consistent with neurophysiologic evidence of upper motor neuron disorders in this population.[10,11]

A combination of within- and between-group comparisons examined the relationship between clinical judgments of voice quality and neuromotor abnormality in SD subjects. The reader will recall that perceptual ratings of strain-strangle voice quality revealed a significant increase in abnormality for the beep..beep and beep..heap tasks as compared to the mid /i/. Similarly, TA activity for the SD subjects was significantly higher than for normal controls on the repeated-word and sentence tasks. Thus, deterioration of voice quality during the more complex speech tasks co-occurs with abnormal increases in TA activity.

In conclusion, this preliminary quantitative analysis of EMG signals supports the hypotheses under test. The findings also yield insights into the complexity of applying quantitative analyses to investigate neuromotor abnormality in SD. For example, SD subjects showed a greater or lesser degree of abnormality relative to our normal controls depending upon the specific measure used to characterize EMG activity for a particular muscle. Effects of this interaction of measure and muscle on between-group differences can be attributed, in part, to three facts. First, we do not know how a specific muscle should function across tasks that range from vegetative to complex linguistic. Indeed, activity of a given muscle may be unconstrained in the motor program for a particular task. In this case, unusually high or low activity may not be an indication of a disorder. Second, we do not know which measure or measures of EMG activity is or are most appropriate to characterize a given muscle during performance of a given task. Finally, the nature of neuromotor abnormality and, hence, the most valid and reliable measure(s) of that abnormality may differ across muscles and/or across tasks within a muscle. Future reports will present analyses of additional tasks, muscles, and measures (eg, including temporal and spectral). Ultimately, our goal is to exploit the analytic power of multiple tasks, muscles, and measures to clarify normal vocal tract neuromotor function and the nature and extent of vocal tract neuromotor abnormality in SD.

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The 1992 Midwinter Meeting of the Association for Research in Otolaryngology will be held February 2-6, 1992, at the Tradewinds Hotel, St Petersburg Beach, Florida. For further information, contact Michele Johnson, Executive Secretary, 900 Des Moines Street, Suite 200, Des Moines, IA 50309; Phone (515) 266-2189, Fax (515) 266-0613.

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CONFERENCE ON ASSISTIVE LISTENING DEVICES
GENERAL ANNOUNCEMENT AND CALL FOR PAPERS

A Conference on Assistive Listening Devices, Tutorials, Applications, and Research will be held June 12-14, 1992, at The University of Iowa, Iowa City, Iowa. For information on registration and accommodation, contact the Conference Center, University of Iowa, Memorial Union, Iowa City, IA 52242; (319) 335-3231, Fax (319) 335-3407. For information on Call for Papers, contact Regina Tisor (319) 356-2471, Fax (319) 356-4547. We have applied for Continuing Education Units from ASHA and HAIC.

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STABLE INTERNAL FIXATION OF FRACTURES OF THE PARTIALLY MINERALIZED THYROID CARTILAGE

JOHN R. AUSTIN, MD
ROBERT B. STANLEY, MD, DDS
DONALD S. COOPER, PHD
LOS ANGELES, CALIFORNIA

Thyroid cartilage fractures due to external blunt trauma have typically been thought to occur in patients over the age of 40. Lack of mineralization of the cartilage has been considered to be the protective mechanism. Our experience with laryngeal injuries has demonstrated that younger persons are indeed at risk for thyroid cartilage fractures, and that these injuries may be easily overlooked. Although these fractures do not lead to laryngeal stenosis if untreated, they may cause noticeable phonatory changes. Fixation of these fractures is difficult because of the usual soft character of the unmineralized cartilage, prompting us to adopt a wire-tube fixation technique. This technique has been uniformly successful in restoring the anatomic contour of the thyroid cartilage, and our results appear to justify open reduction of these moderately displaced or angulated thyroid cartilage fractures.

KEY WORDS — fixation, fracture, thyroid cartilage.

Fractures of the thyroid cartilage have traditionally been described as occurring most often in individuals over the age of 40.[1,2] In childhood, the poorly mineralized thyroid cartilage appears to be protected from injury by its inherent flexibility and pliability.[3,4] These protective characteristics are thought to persist even into the third and fourth decades of life, and Yerman et al[5] have confirmed that calcification is not present in the thyroid cartilage until the age of 20. The mineralization process then begins at the posterior and inferior borders of each lamina and progresses superiorly in an unpredictable manner. The progression may be bilaterally asymmetric and the central lamina may be spared completely. Our recent experience with laryngeal injuries due to external blunt trauma has allowed us to make in vivo observations that paradoxically confirm the postmortem findings of Yerman et al and disprove the accepted opinion that the poorly mineralized thyroid cartilage is at low risk for fracture. Additionally, we have found that reduction and stabilization of fractures in these younger larynges may be more difficult than in older, heavily calcified larynges. Our experiences will be presented to demonstrate both the nature of thyroid cartilage fractures in young adults and a fixation technique that appears to give superior results in these patients.

STUDY GROUP

From January 1, 1984, to December 31, 1989, 215 patients with a history of recent blunt trauma to the neck were evaluated with computed tomography (CT) for possible laryngeal cartilage fracture at the Los Angeles County–University of Southern California Medical Center. The indications for obtaining the scans are listed in Table 1. Excluded from the study, therefore, were patients who suffered severe disruption of the laryngeal framework and internal soft tissues (thus requiring emergent tracheostomy and neck exploration) due to ultra-high-speed deceleration impact forces that would crush even the most resilient of cartilaginous structures. Also excluded were patients with a suspected laryngeal injury who were taken emergently to the operating room for care of other life-threatening problems. Typically, these patients underwent direct endoscopic evaluation and neck exploration during the same session of general anesthesia. The study group therefore includes patients with a "suspected" laryngeal fracture, and admittedly includes some patients who fall well within the criteria established by some trauma surgeons[6,7] for mandatory exploration and some patients whose further evaluation was prompted only by the current medicolegal environment.

The results are summarized in Tables 2 and 3. Twenty-three (52%) of the total group of 44 fracture victims were 30 years of age or younger. Of the fractures that occurred in this younger subgroup, 18 were of the thyroid cartilage, 3 of the cricoid carti-

TABLE 1. INDICATIONS FOR OBTAINING COMPUTED TOMOGRAPHIC SCAN OF LARYNX FOLLOWING BLUNT NECK TRAUMA

Tracheostomy performed at another facility for stabilization prior to transfer, or by resident staff to protect airway prior to further evaluation
Edema and/or hematoma or ecchymosis visible in endolarynx or pyriform sinus on indirect examination
Small lacerations or blood visible in endolarynx on indirect examination
Altered vocal cord mobility
Palpation of external landmarks suspicious for fracture
Voice alterations noted by examiner or claimed by patient

From the Department of Otolaryngology–Head and Neck Surgery, University of Southern California School of Medicine, Los Angeles, California.

Presented at the meeting of the American Laryngological Association, Waikoloa, Hawaii, May 4-5, 1991.

REPRINTS — Robert B. Stanley, Jr, MD, DDS, Dept of Otolaryngology–Head and Neck Surgery, 1200 N State St, Box 795, Los Angeles, CA 90033.

TABLE 2. AGE DISTRIBUTION OF PATIENTS EVALUATED FOR SUSPECTED LARYNGEAL INJURY

	No.	*Average Age (y)*	*Age Range (y)*
Patients evaluated	215	30.4	4-65
Patients with fractures	44	29.5	16-53

lage, and 2 of both cartilages. Among the patients in this group with a fracture of the thyroid cartilage (with or without a cricoid cartilage fracture), none had derangement of the glottic and/or supraglottic soft tissues deemed severe enough to warrant thyrotomy and repair. None of the thyroid cartilage fractures in this group were comminuted, but rather most were moderately displaced or angulated single linear fractures that would not be expected to lead to acute airway obstruction or chronic laryngeal stenosis. However, we have developed an aggressive management philosophy for these types of injuries, based on previous clinical and laboratory observations.[8,9] These studies showed that even minimally displaced or angulated fractures of the thyroid laminae can produce alterations in the glottic configuration sufficient to disrupt the normal laryngeal valving mechanism. These changes produce increases or decreases in glottic resistance, dependent on the orientation of the displaced cartilage segments, and thus may produce noticeable if not debilitating phonatory disorders.

Once this aggressive policy was adopted, we were faced with the realization that standard reduction and fixation techniques using stainless steel wires or nonabsorbable sutures placed in a simple or figure-eight pattern were inadequate for holding a reduction. Although edge-to-edge contact could be maintained between the fragments, healed lateral fragments tended to be angulated and healed midline fractures tended to be flattened (as seen on postoperative CT scans). Overtightening of the wires in an attempt to hold the reduction invariably caused the wires to cut through the poorly mineralized cartilage. Similarly, the use of miniadaptation plates and screws from the maxillofacial trauma armamentarium failed to produce acceptable results when used on the soft cartilage.

TABLE 3. SITE OF LARYNGEAL CARTILAGE FRACTURE BY AGE (44 PATIENTS)

	Age (y)					
Cartilage	*0-10*	*11-20*	*21-30*	*31-40*	*>40*	*Total*
Thyroid	0	6	12	8	4	30
Cricoid	0	1	2	4	2	9
Thyroid and cricoid	0	0	2	2	1	5

We now use a technique that splints the fractures with fine wires passed through the lumina of blunted needles that are placed as battens to span the fractures. Occasionally, temporary translaryngeal wires will be used to reduce a severely flattened angle between the lateral laminae when a midline fracture is present. The technique is schematically demonstrated in Figs 1 and 2, and will also be demonstrated clinically in the following case reports. It has been successfully used in seven patients, and the success and ease with which it has been used have prompted us to apply it to all thyroid cartilage fractures, even comminuted injuries in older, more mineralized larynges.

CASE REPORTS

Case 1. A 28-year-old man suffered blunt neck trauma in a motor vehicle accident. He presented with acute dysphonia, mild endolaryngeal edema, and a hematoma in the right vocal cord. No lacerations of the mucosa were noted. He was started on a regimen of steroids and antibiotics, but 12 hours later the edema was felt to be sufficient to warrant securing of the airway with a tracheostomy. A CT scan revealed a displaced fracture of the right thyroid lamina (Fig 3A), and 2 days later the fracture was repaired by the technique shown in Fig 1. The patient was decannulated rapidly and he obtained an excellent voice that allowed him to return to singing in his church choir, although he did complain of occasional difficulty reaching high tones while singing. The reduced fracture is shown on a follow-up scan in Fig 3B.

Case 2. A 30-year-old male musician and singer was strangled with a forearm choke-hold. He presented with a complaint of a weak breathy voice

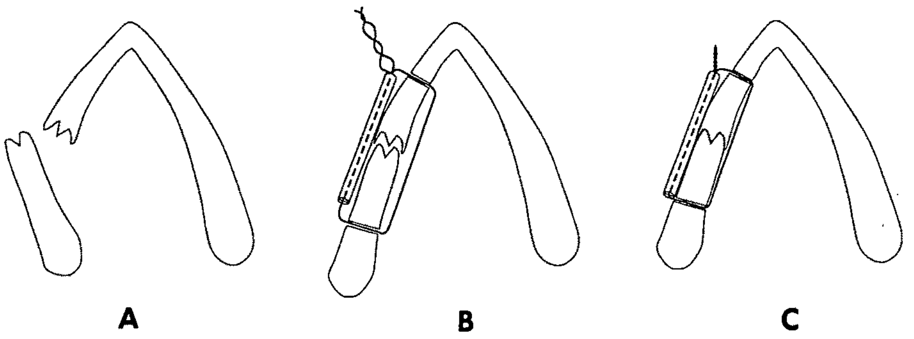

Fig 1. Schematic drawing of wire-tube technique. A) Displaced lateral lamina fracture. B) Wire passed through blunted 18-gauge needle and through cartilage in horizontal fashion. Wire and tube will remain in place permanently; therefore, endolaryngeal aspect of wire must be passed submucosally. C) Although wire may cut through cartilage immediately adjacent to needle hole, forces are distributed over broad enough area to prevent complete pull-through of wire. For lateral fracture, two wire-tube devices should be placed, one above and one below level of true vocal cord.

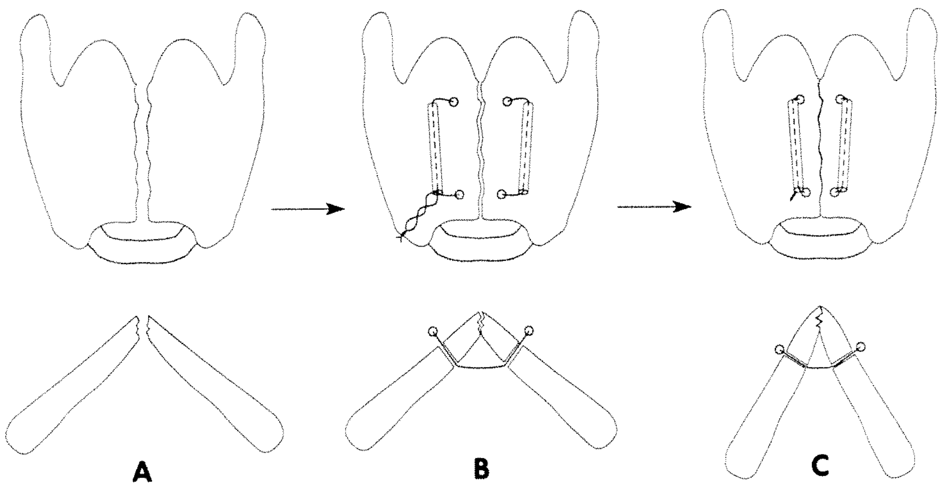

Fig 2. Schematic drawing of wire-tube technique for midline cartilage fracture. A) Midline fracture with flattened lamina. B) Wire passed in translaryngeal vertical mattress fashion. C) Wire secured with approximation and fixation of fracture with normal alignment of laminae. Although upper translaryngeal crossing of wire should be in preepiglottic space, lower crossing may be intraluminal at subglottic level. Removal in 2 to 3 months is therefore recommended.

and dysphagia but no airway distress. Indirect examination revealed a mobile right true vocal cord that appeared to be bulging medially and superiorly, but had no ecchymosis (Fig 4A). A CT scan demonstrated midline and right thyroid lamina fractures (Fig 5A). Although persistent edema could not be ruled out as being partially responsible for the bulging appearance of the cord, repair was undertaken to restore the contour of the thyroid cartilage. This decision was based on the observation that the position of the displaced fragment matched exactly a situation examined in the previously mentioned laboratory study,[9] and closely resembled the desired anatomic result of a thyroplasty intended to medialize the cord. Fixation was achieved with the wire-tube technique (Figs 1 and 2), restoring alignment of the cartilage as well as position and dimension of the vocal cord (Fig 4B). A tracheostomy was performed to facilitate reduction of the fragments, and the patient was easily decannulated several days later. A postoperative CT scan shows the stable reduction (Fig 5B). The patient claims a normal voice and has returned to professional singing.

Case 3. A 43-year-old woman was bitten on the neck by her horse during a grooming session. She noted immediate dysphagia and dysphonia but no respiratory distress. A tracheostomy was performed at another hospital 6 hours later when the patient was unable to breathe comfortably while supine. A CT scan demonstrated vertical fractures of the thyroid cartilage (Fig 6A). The fractures were reduced 3 days later by the wire-tube technique (Figs 1 and 2). Of note, the midline fracture was of the greenstick variety through an area that demonstrated little if any mineralization. Restoration of a more normal angle between the lateral laminae required translaryngeal wires (Fig 6B), and the tracheostomy was left in place in anticipation of subsequent removal of the wires under general anesthesia. A follow-up CT scan at 3 months revealed a stable reduction of the fractures, and the translaryngeal wires were removed. The patient now has a normal-appearing larynx with no evidence of endolaryngeal damage related to the translaryngeal wires. She has no complaints of voice change.

DISCUSSION

Liberal use of CT scanning in the evaluation of patients suffering blunt external trauma to the larynx has allowed us to show that the relatively low levels of mineralization in their thyroid cartilage do not protect young adults from fractures of this structure. Although members of this age group are occasionally seen with severe, comminuted crush in-

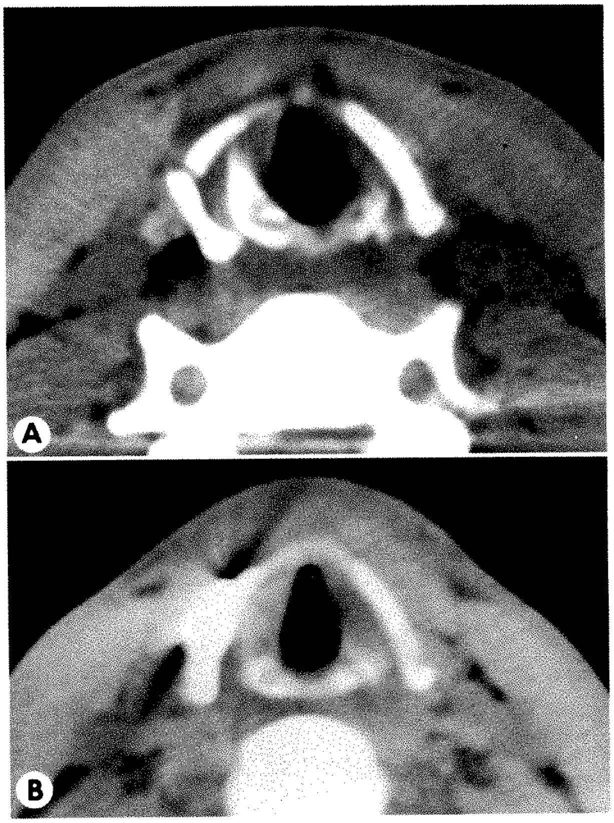

Fig 3. (Case 1) Computed tomograms. A) Preoperative scan showing displaced and angulated fracture of right thyroid lamina. B) Postoperative scan showing return of laryngeal symmetry. Artifact on film is scatter of x-ray beam by horizontally positioned wire-tube device.

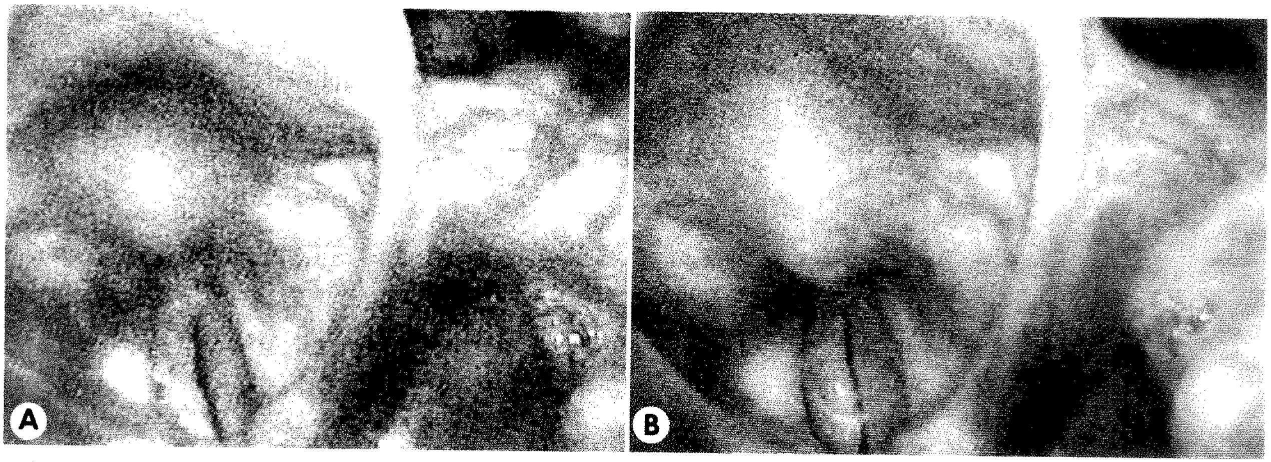

Fig 4. (Case 2) Photographs taken from videolaryngoscopy. A) Preoperatively, right true vocal cord has appearance of medialized cord and glottis is bowed to left. B) Postoperative photograph reveals symmetric cords and straight glottis.

juries due to high-speed deceleration events, many more appear to suffer linear, moderately displaced or angulated fractures due to lower-impact forces. More than one fracture line may be present, but endolaryngeal mucosa lacerations usually do not accompany these injuries, and the need for an emergent tracheostomy is unusual. Therefore, many of these injuries will go undetected initially if the otolaryngologist does not have a high index of suspicion and does not use CT scanning to evaluate the patient on the basis of criteria similar to those used at our institution. Patients in whom such an injury is overlooked most likely will not develop laryngeal stenosis or suffer marked changes in phonation. However, it is clear that these less severe injuries can modify the glottic configuration sufficiently to alter the more subtle aspects of phonation, includ-

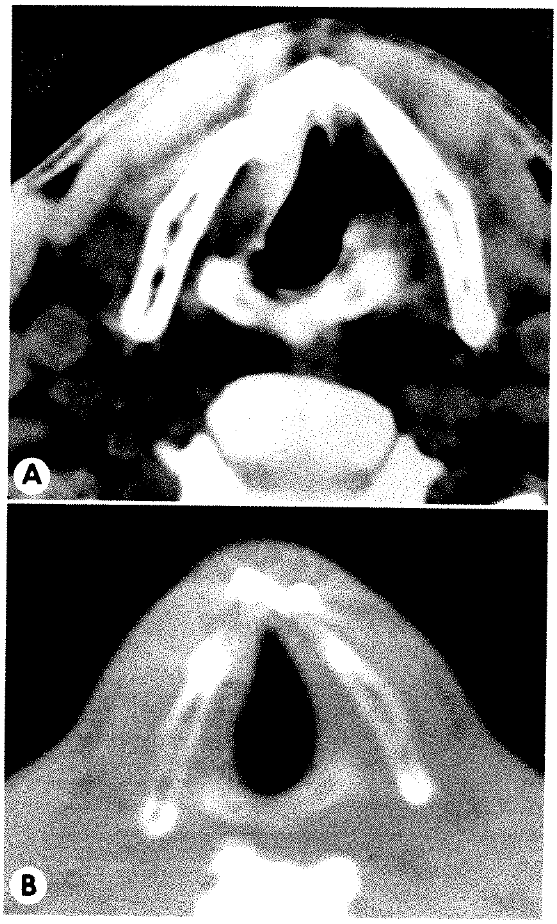

Fig 5. (Case 2) Computed tomograms. A) Fractures have resulted in medial displacement of anterior third of right thyroid lamina in manner that resembles thyroplasty for vocal cord medialization. B) Early postoperative scan shows realignment of laminae. Different window was used because of scatter from stainless steel needles.

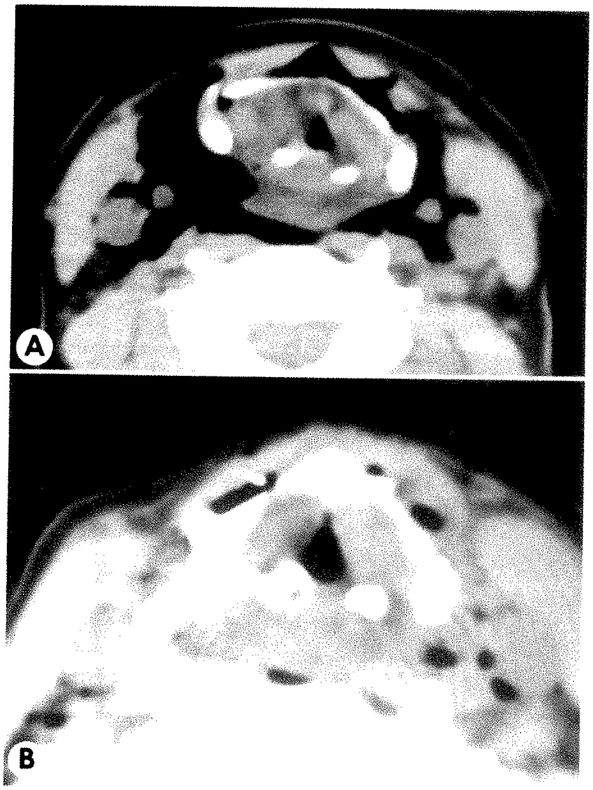

Fig 6. (Case 3) Computed tomograms. A) There is almost total flattening of angle between lateral laminae. B) Early postoperative scan with translaryngeal wires visible immediately above level of anterior commissure. More normal interlaminal angle has been restored.

ing mean frequency and frequency range. Although such perturbations might not be a problem in day-to-day conversational speech, noticeable difficulties might arise for the public speaker or singer.

Justification for an aggressive surgical approach in management of these injuries requires that an accurate, stable reduction be achieved. The wire-tube fixation technique has allowed us to achieve uniformly good results in stabilizing fractures of even poorly mineralized thyroid cartilages, as demonstrated by the anatomic reductions on postoperative CT scans, symmetric vocal cord appearance on videolaryngoscopy, and, most important, by patients' satisfaction with their speaking and singing voices. We therefore urge that the otolaryngologist have a high index of suspicion for fractures of the thyroid cartilage following blunt neck trauma, even in patients less than 40 years of age, previously thought to be at low risk. High-resolution CT scanning can demonstrate previously undetectable thyroid cartilage fractures, and treatment of those fractures can offer the patient an improved chance of regaining a near-normal if not normal voice.

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INJECTION AND REMOVAL OF TEFLON FOR UNILATERAL VOCAL CORD PARALYSIS

HERBERT H. DEDO, MD

SAN FRANCISCO, CALIFORNIA

For over 70 years, reinnervation attempts have been unsuccessful in restoring motion to paralyzed vocal cords, in spite of occasional claims to the contrary. Fortunately, the major defect of unilateral vocal cord paralysis, a soft and breathy voice, can be eliminated if the edge of the paralyzed vocal cord is moved to the midline. This permits the mobile vocal cord to adduct and therefore to vibrate firmly against the edge of the paralyzed vocal cord during phonation, eliminating the air leak between the vocal cords. Teflon injection of the paralyzed vocal cord does this effectively. It is accomplished most easily and reliably via indirect laryngoscopy under local anesthesia, so the effect on the voice can be monitored during the injection. Teflon can be easily removed from the vocal cord via direct laryngoscopy. The disadvantages of trying to medialize the edge of a paralyzed vocal cord via a window in the thyroid cartilage (laryngeal framework surgery) will be discussed.

KEY WORDS — laryngeal framework surgery, medialization, neuromuscular grafts, recurrent laryngeal nerve paralysis, superior laryngeal nerve paralysis, Teflon injection, vocal cord.

PROBLEM

Two distinct categories of unilateral vocal cord paralysis exist: pure recurrent laryngeal nerve (RLN) paralysis and RLN plus superior laryngeal nerve (SLN) paralysis. These differences, plus variation in paralyzed vocal cord muscle atrophy and contracture and compensation by the mobile vocal cord, explain the variations seen in paralyzed vocal cord shape and position, and therefore voice breathiness and weakness both before and after medialization of the edge of the paralyzed vocal fold. Unilateral RLN paralysis leaves the ipsilateral vocal cord in the paramedian position (Fig 1A-D) and RLN + SLN paralysis places the edge more laterally in the intermediate position (Fig 1E,F).[1] With RLN paralysis during phonation, however, the arytenoid of the paralyzed vocal cord still adducts 1 to 2 mm and closes the posterior third of the glottis because of cricothyroid muscle plus interarytenoid muscle contraction (Fig 1D). With RLN + SLN paralysis, the ipsilateral cricothyroid muscle is also paralyzed, so only the partial interarytenoid muscle contraction remains, because half its motor nerve supply is still available from the intact RLN, to partially adduct the posterior edge of the arytenoid. As a result, in RLN + SLN paralysis the arytenoid drifts slightly laterally from the midline (Fig 1E,F). This leaves a 2-mm gap or chink between the arytenoids during phonation. Also, there is a wider chink between the membranous vocal cords, because the closing and tensing action of the cricoarytenoid muscle is lost and there is more vocal cord atrophy (and thus thinning) when both the SLN and RLN are paralyzed. Therefore, more air leakage, weakness, breathiness, and diplophonia — or, in some patients, paralytic falsetto (from overcompensation by the mobile cord) — occur during phonation in patients with RLN + SLN paralysis than in those with RLN paralysis alone.

Since medialization of the membranous vocal cord with Teflon injection, laryngeal framework surgery, or neural grafts cannot close this posterior gap or chink, voice results in RLN + SLN paralysis patients usually are not quite as good as in patients with pure RLN paralysis. This has not been emphasized enough, so surgeons and patients have not been prepared to accept a slightly breathy phonatory voice as being a good result in these combined RLN + SLN paralysis cases. If the patient wishes, the posterior third chink can still be treated with arytenoid medialization.[2] The improvement in RLN + SLN patients is usually more dramatic than in RLN patients, since their voice starts from a much worse level — often only a very breathy stage whisper. They are usually delighted with the result and do not wish an open operation. The typical result after medialization in pure RLN paralysis is a voice improvement from a mildly or moderately breathy phonatory voice to a clear, nonbreathy, phonatory one. Diplophonia and paralytic falsetto, if present, can also be eliminated if Teflon injection is performed correctly. Since surgeons generally have not been trying to identify whether an apparently paralyzed vocal cord is due to paralysis of the RLN or RLN + SLN (or cricoarytenoid joint fixation), they have not prepared themselves or their patients for the possibility that the patient's breathy, weak voice may be improved, often dramatically, but not made fully normal by medialization of the paralyzed membranous vocal cord.

Some doctors — whose patients have subsequent-

From the Department of Otolaryngology-Head and Neck Surgery, University of California, San Francisco, California.

Presented at the meeting of the American Laryngological Association, Waikoloa, Hawaii, May 4-5, 1991.

REPRINTS — Herbert H. Dedo, MD, Dept of Otolaryngology-Head and Neck Surgery, University of California, San Francisco, 400 Parnassus Ave, A735, Box 0342, San Francisco, CA 94143-0342.

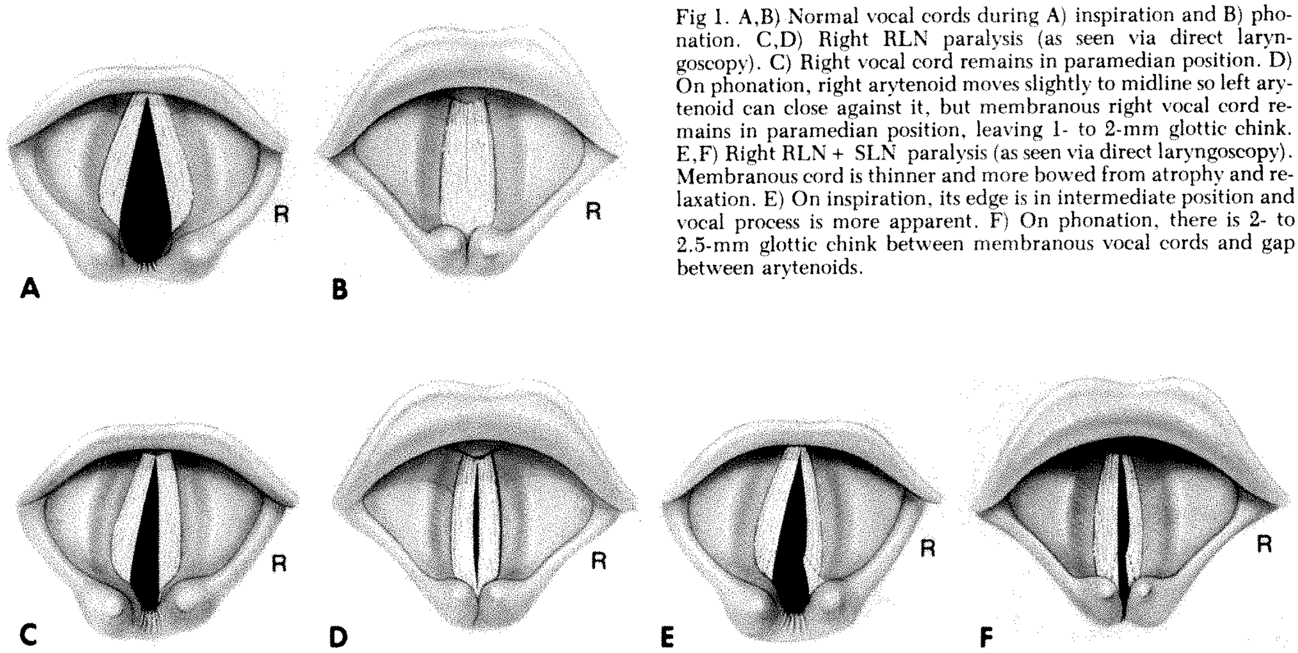

Fig 1. A,B) Normal vocal cords during A) inspiration and B) phonation. C,D) Right RLN paralysis (as seen via direct laryngoscopy). C) Right vocal cord remains in paramedian position. D) On phonation, right arytenoid moves slightly to midline so left arytenoid can close against it, but membranous right vocal cord remains in paramedian position, leaving 1- to 2-mm glottic chink. E,F) Right RLN + SLN paralysis (as seen via direct laryngoscopy). Membranous cord is thinner and more bowed from atrophy and relaxation. E) On inspiration, its edge is in intermediate position and vocal process is more apparent. F) On phonation, there is 2- to 2.5-mm glottic chink between membranous vocal cords and gap between arytenoids.

ly required partial Teflon removal — have injected too much Teflon either initially or later in their mistaken attempt to close the posterior-third gap between the arytenoids and to stop the breathiness (Fig 2). Posterior glottic closure is impossible with Teflon overinjection of the membranous cord. Instead, a bigger posterior gap is created, because the mobile cord is held back by the bulging paralyzed vocal cord and the vibration of the mobile cord is interfered with so that the voice is made husky and coarse, or gravelly. Failure to recognize and accept the limitations of medialization of the membranous portion of a paralyzed vocal cord has not only caused surgeons to overinject cords, it has also caused them to change from Teflon injection to insertion of cartilage or silicone rubber into the paralyzed vocal cord via an open neck incision (laryngeal framework surgery),[2,3] or to attempt laryngeal reinnervation.[4,5] Laryngeal framework surgery and reinnervation have been criticized as being less reliable, being harder on the patient, requiring Gelfoam injection,[6] and costing more than Teflon injection, while they do not provide a better voice. Initially, it was hoped that reinnervation would achieve remobilization of a paralyzed vocal cord. Now it is acknowledged that reinnervation does not achieve normal mobility,[6] and at best it may only medialize the edge of the cord so slightly after many months[5-12] that it has still been necessary to inject Gelfoam into the vocal cord.[6] In my experience, neural or neuromuscular grafting has not medialized the paralyzed vocal cord edge as reliably, inexpensively, and rapidly or as easily for the patient as Teflon injection via indirect laryngoscopy[12,13] — even when performed by its proponents in patients I have seen later.

CLASSIFICATION OF VOICE ABNORMALITY CAUSED BY UNILATERAL VOCAL CORD PARALYSIS

I use the following informal system to classify the degree or type of hoarseness caused by vocal cord paralysis. Incomplete or weak closure of the mobile vocal cord edge with the edge of the paralyzed vocal cord during phonation causes a voice weakness (poor projection or softness) and breathiness because of the air leakage between the vocal cords during phonation. If a large enough glottic chink or incompetence (2 to 3 mm at the widest point between vocal processes of arytenoids, usually from RLN + SLN paralysis) is present so one or both vocal cords fail to be thrown into vibration or oscillation, a pure whisper or white noise type 4 voice will result. If there is a slightly narrower chink, with some vibration of at least one vocal cord releasing puffs of air plus white noise from the continuous air leak, there will be a stage whisper (ie, whisper and some actual phonation) or a type 3 voice. This may be seen in an early pure RLN paralysis, but in a late paralysis (after 4 to 6 months of compensation) it is usually a result of RLN + SLN paralysis.

If there is a narrower gap during phonation (1 to 2 mm), a moderately breathy phonatory type 2 voice will result. If the mobile cord appears to close against the paralyzed vocal cord so no glottic chink is visible, but the closure is weak, the voice will be a slightly breathy phonatory type 1 voice, especially when the patient is fatigued or has been talking very much.

A soft normal or solid (ie, nonbreathy) phonatory voice occurs when the vocal cords close firmly enough between each vibration to prevent constant

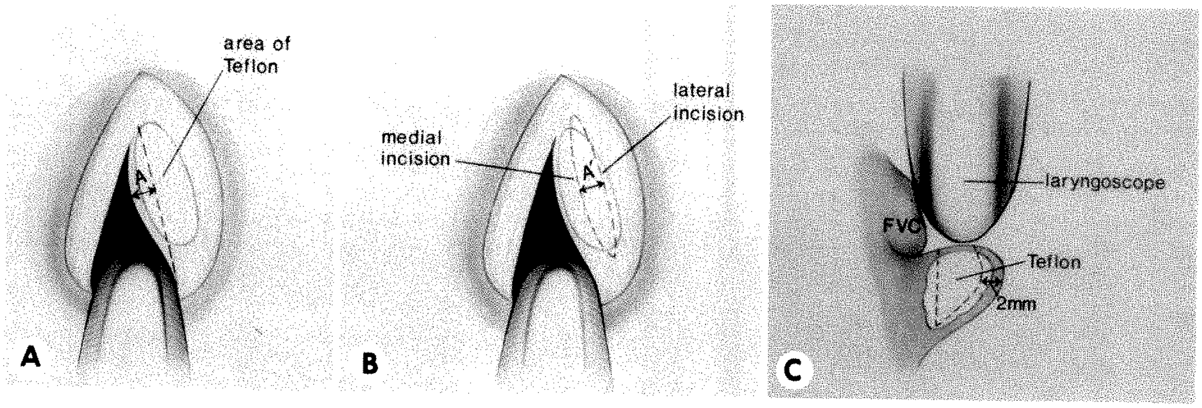

Fig 2. Teflon overinjection. A) Convexity is distance free edge of cord projects medial to line drawn from anterior commissure to lateral edge of endotracheal tube. B) Width of wedge resection equals width of convexity. Resection stops just at anterior and posterior edges of Teflon. C) Wedge resection stops at bottom edge of Teflon and preserves 2 mm of medial edge of cord to maintain viability and stiffness so it will not be pulled medially and block airway during inspiration. FVC — false vocal cord.

air leak and breathiness. This can be present because of unusually good compensation by the mobile vocal cord, but is rare in untreated unilateral RLN paralysis, especially late in the day. A normal voice requires firm closure of the vocal cord edges to allow normal subglottic pressure to be achieved, and therefore normal volume to be reached, during phonation.

A paralytic falsetto (abnormally high fundamental speaking frequency) voice occurs when the mobile vocal cord overcompensates while closing the chink, so while it eliminates the air leak and breathiness, it is stretched so tightly that its frequency of vibration is elevated above normal.

Diplophonia is the production of a harsh, husky, or gravelly voice that sounds as if there is mucus on the vocal cords when none is seen on indirect laryngoscopy. It is the result of the lesser mass and tension in the paralyzed vocal cord, causing it to vibrate at a lower frequency than the normal vocal cord.

SOLUTION

Since normal motion cannot be surgically restored to a paralyzed vocal cord,[6] effective treatment requires its edge to be repositioned medially. If the edge of a paralyzed vocal cord is moved to the straight midline position, the air leak and therefore the breathiness and weakness (or paralytic falsetto, if present) will be eliminated. A near-normal or normal phonatory voice will be achieved because one or both vibrating vocal cords will be letting out strong puffs of air. If paralytic falsetto is present, it will be lowered or eliminated because the mobile, intact vocal cord will not have to be pulled so tight longitudinally in compensation. If diplophonia persists, injection of a little more Teflon to stop the abnormal vibration of the paralyzed vocal cord can eliminate it.

Three basic approaches have been used to medialize the edge of the paralyzed vocal cord: distal RLN anastomosis to proximal RLN or other motor nerves, or insertion of neuromuscular grafts into intrinsic laryngeal muscles; widening the paralyzed vocal cord by injecting Teflon; or inserting cartilage, silicone rubber, or other materials lateral to the paralyzed cord via a hole cut in the thyroid cartilage.

Anastomosis of the ends of the severed RLN or of the distal RLN to another motor nerve in the area has been performed in humans by many surgeons for more than 70 years (when the severed ends could be found and joined) without restoring effective adduction during phonation, although resting tone may be improved after many months.[5-11] Visible adduction during phonation could not be achieved after prolonged follow-up, even when 16-0 monofilament nylon sutures and microsurgical techniques were used under ideal conditions on freshly cut RLNs in dogs.[12]

Neuromuscular grafts from local motor nerves and insertion of their motor end plates into laryngeal muscles have not recovered effective motion or reliable repositioning. The ansa hypoglossi-omohyoid[4] has been anastomosed into the posterior cricoarytenoid muscle for bilateral RLN paralysis in the hope of opening a paralyzed vocal cord during inspiration. Vagus, ansa hypoglossus, and phrenic nerve fibers or motor end plates have been inserted into the thyroarytenoid muscle to try to achieve adduction during phonation. These procedures have failed to reliably restore effective or useful motion that is visible on indirect laryngoscopy or on film — even when performed by the proponents of reinnervation.[4,5,11,13] Lately, some authors have admitted that normal motion was not regained from nerve transfer, but they claimed increased tone moved the vocal cord edge medially.[6] If it was so effective, however, why was it necessary in addition to inject Gelfoam into the vocal cord? Based on the results I have seen, reinnervation is neither consistent nor reliable.[13]

The most reliable, effective technique for achiev-

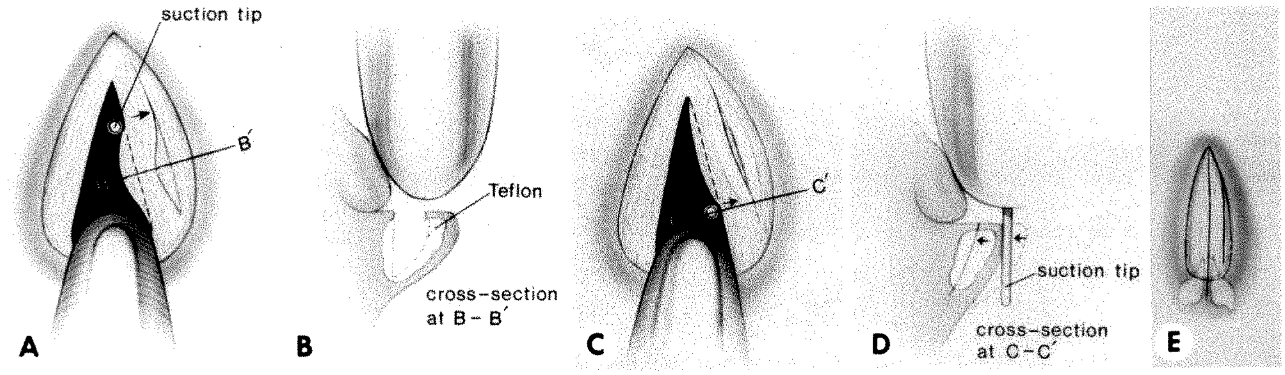

Fig 3. A-D) Teflon is removed until collapse of width of cleft created by wedge resection with suction tip puts free cord edge along straight line from anterior commissure to edge of endotracheal tube. E) When healed, right vocal cord edge is straight and midline, and mobile cord meets it well.

ing the best voice for a patient with unilateral vocal cord paralysis is to install material in the lateral portion of the paralyzed vocal fold to widen it and to push its free edge medially. This can be done by injecting Teflon via indirect laryngoscopy or with laryngeal framework surgery, in which cartilage[2] or silicone rubber wedges[2,3] are installed through a window made in the thyroid cartilage.

Teflon injection and insertion of cartilage or silicone rubber wedges in the lateral portion of the membranous vocal cord are similar in that they do not medialize the arytenoid because it is posterior to the area that can be augmented.[2,13] Also, if a large amount of foreign material is installed, the free edge of the paralyzed vocal cord will not vibrate, although this will not hurt the voice if the edge of the cord ends up straight and midline and if the mobile cord is normal. Since cartilage or silicone is placed lateral to the vocal cord, however, the cord can vibrate if a small amount is placed. Teflon also is injected lateral to the vibrating edge, and if the correct amount is used, the edge can vibrate just as well in synchrony with the mobile vocal cord. Both procedures require considerable experience with the technique and attention to detail to get the best results.

The laryngeal framework approach has several disadvantages. Installing silicone or cartilage wedges through a hole made in the thyroid cartilage requires a neck incision. The procedure usually takes more than an hour, allowing edema to accumulate in the vocal cord and causing difficulty in judging how large a block of foreign material to install, as well as prolonging patient discomfort. Increasing or decreasing the medialization of the cord edge subtly and rapidly is difficult. The relatively large block of foreign material can be displaced or become infected, necessitating removal through another open neck operation. The vocal cord must be observed through a fiberoptic laryngoscope, which gives a grainy, less precise view of the vocal cord edge than a mirror examination does on indirect laryngoscopy. The patient must be lying down under a drape, possibly sedated or under a general anesthetic; hence, evaluating the effect on the voice of the insertion of a given size wedge of silicone rubber or cartilage is more difficult than with Teflon injection via indirect laryngoscopy with the patient sitting up. Removal and replacement with a larger wedge is difficult because it requires another open operation. In addition, the procedure is two to three times as expensive as Teflon injection.

Advantages of Teflon Injection. I prefer Teflon injection via indirect laryngoscopy because it only takes about 10 minutes — 9½ minutes to topically anesthetize and a few seconds to inject — using the technique shown in detail in my surgical atlas.[13] Thus, it is easier on the patient and can be completed before edema distorts the vocal cord. This is important because subtle edema starts to accumulate in the paralyzed vocal cord within 2 to 5 minutes after the first needle insertion. If there is delay in completion of the medialization, this causes difficulty in seeing and hearing whether the correct amount of medialization has been achieved. Using Teflon paste, the vocal cord can be gradually widened by very small (0.1 mL) increments until the cord edge is midline while it is seen clearly and well in the mirror. Then the needle is withdrawn to a point just above the cord so it will not cause distortion, the patient is asked to say "he" or "ho," and the effect on the vocal cord and voice quality is confirmed by auditory perception. If a little more Teflon is required, it is injected and then the undersurface bulge is massaged back with the needle shank.[13]

The injected Teflon is in microscopic particles, so it is well tolerated by the tissues.[14] (I have only seen late convexity develop in the cord edge in 2% to 3% of patients.) The patient is sitting up and is not under a drape, so he or she can phonate and talk normally and easily. Teflon injection is cost-effective. If necessary (eg, if too much is injected, cord motion returns, or a rare, small intracordal granuloma develops), the Teflon is easily removed partially or completely via direct laryngoscopy[13,15] without a neck incision (Figs 2 and 3). If enough

Teflon is injected to stop vibration of the edge of the paralyzed vocal cord, eg, to eliminate diplophonia, a normal voice can still be achieved, provided the edge of the paralyzed vocal cord is straight and midline (Fig 3E) and the mobile cord has normal vibration. It is not necessary for the edge of the paralyzed vocal cord to vibrate to achieve a normal voice!

DISCUSSION

Augmentation or medialization of a paralyzed vocal cord (or one of a pair of bowed mobile vocal cords, as can occur in the elderly) is a form of vocal plastic surgery or phonosurgery. The unwanted vocal characteristics such as breathiness, weakness, paralytic falsetto, or diplophonia can be decreased or eliminated in a graded fashion that must be matched to the severity of the voice abnormality. Vocal cord medialization is similar to facial plastic surgery, liposuction, or breast augmentation in that the amount of material added or subtracted is important. In fact, in the vocal cord a one-drop difference in injected volume and a 1- to 2-mm difference in location of the paralyzed cord edge can have a large effect on the voice. As with surgery in general and plastic surgery in particular, the correct selection of patients and a precise surgical technique are very important in phonosurgery. Straightening and moving the medial edge of the vocal cord 1 to 2 mm to the midline can dramatically improve the voice, but bulging it 1 to 2 mm past the midline can eliminate the improvement and cause a rough and husky or gravelly voice that may be a disappointment.

The difficult part of Teflon injection via indirect laryngoscopy is developing eye-hand facility in inserting the curved needle into the vocal cord lateral to the vocal process of the arytenoid while looking at it in a laryngeal mirror. This is because the mirror image makes the needle appear to move to the right when the eye and hand try to move it to the left. This skill can be learned in vitro, however, by practicing with a headlight and laryngeal mirror while moving and positioning a curved Teflon injection needle on a Bruening syringe (Storz Instrument Co, St Louis, Mo) into a vocal cord drawn on a rubber glove or a piece of chicken breast placed in a small can.

The amount to be injected (usually only two to four clicks) is relatively easy to determine by watching the vocal cord edge and listening to the decreasing breathiness and increasing voice strength and clarity during trial phonations as this edge is moved to the straight midline position, allowing the mobile cord to close against it firmly. The skills required in installing the correct size, shape, and location of a cartilage or silicone rubber insert via a hole in the thyroid cartilage are not practiced so easily in vivo or in vitro.

I do not inject collagen into the vocal cord anymore because it is absorbed in 2 to 3 months and thus requires reinjection every few months. Injection of Gelfoam causes scarring within the vocal cord and is not desirable for temporary relief while seeing if a nerve may recover. Recurrent laryngeal nerve paralysis rarely recovers, with the exception of an occasional recovery after spontaneous paralysis or carotid artery endarterectomy or anterior cervical fusion when the nerve was just bruised by a retractor. Furthermore, there is no reason in these rare cases to expect the Gelfoam to be absorbed just when neural function returns. I have injected Teflon when there is a small chance of spontaneous recovery of motion and the patient cannot wait 6 to 12 months (eg, because of aspiration or loss of a job due to a weak voice). In two of my cases in which the paralysis cleared, the Teflon was removed without losing cord motion.[13,15]

SUMMARY

Neural or neuromuscular anastomosis and framework surgery do not restore normal vocal cord motion and at best may increase thyroarytenoid muscle tone and volume slightly. If these techniques do improve a voice, open surgery is required, which is more extensive, prolonged, expensive, and less reliable than Teflon injection done correctly. Also, with neural anastomosis or neuromuscular grafts, months — not minutes — will pass before voice improvement occurs, if it does. These patients may still need injection of material into the paralyzed cord to achieve proper medialization.

Teflon injection can be technically challenging at first for the surgeon. In my opinion, which is based on performing more than 400 Teflon vocal cord injections via indirect laryngoscopy and 8 via direct laryngoscopy under general anesthesia (required because of severe gagging, vertigo, paraplegia, etc), this is the easiest (for the patient), safest, most reliable, and most effective available means of restoring the best possible voice after unilateral vocal cord paralysis. Very small increments of Teflon can be injected while the surgeon observes the vocal cord and listens to the patient's voice to determine the correct end point. Then the inferior surface of the vocal cord can be molded slightly with the side of the needle as necessary, because the vocal cord is plastic until fibrosis fixes the Teflon particles in place 2 to 3 weeks postoperatively. If the minimum required amount of Teflon is placed laterally and posteriorly in the membranous paralyzed vocal cord, the free edge of the cord will vibrate in synchrony with the normal cord, although vibration of the edge of the paralyzed cord is not necessary to create a clear, solid phonatory voice. Teflon can easily be partially or completely removed later via direct laryngoscopy, if necessary.

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EFFECT OF PRIOR ANTIBIOTIC TREATMENT ON MIDDLE EAR DISEASE IN CHILDREN

HOWARD FADEN, MD
JOEL BERNSTEIN, MD
JOHN STANIEVICH, MD
LINDA BRODSKY, MD
PEARAY L. OGRA, MD
BUFFALO, NEW YORK

The effect of prior antibiotic treatment on the course of otitis media was assessed in a group of 62 children who experienced 83 episodes of ear infection during 3 years of observation. Bacterial quantitation in middle ear fluids demonstrated a significantly higher colony count in symptomatic children ($3.9 \times 10^4 \pm 12$ bacteria per milliliter) compared to asymptomatic children ($6.3 \times 10^3 \pm 10$ bacteria per milliliter; $p = .05$). Bacterial counts similarly tended to be higher in children with *Streptococcus pneumoniae* ($4.0 \times 10^6 \pm 16$ bacteria per milliliter) and *Hemophilus influenzae* ($2.0 \times 10^6 \pm 16$ bacteria per milliliter), who were more often symptomatic (73% and 55%, respectively, versus 38%) than children with *Moraxella catarrhalis* ($7.9 \times 10^3 \pm 2$). Antibiotic therapy between 3 and 30 days prior to bacterial diagnosis was associated with a reduction in symptoms from 70% to 38% ($p < .025$). However, prior treatment did not statistically reduce bacterial colony counts, although *S pneumoniae* decreased 90% in the previously treated group. Resistance to ampicillin occurred in 0% of *S pneumoniae*, 39% of nontypeable *H influenzae*, and 80% of *M catarrhalis* subjects without prior treatment and in 0%, 46%, and 100%, respectively, of subjects previously treated ($p < .025$). These data suggest that prior treatment has a significant impact on the subsequent course of otitis media in children.

KEY WORDS — antibiotics, *Hemophilus influenzae*, microbiology, *Moraxella catarrhalis*, otitis media, *Streptococcus pneumoniae*.

INTRODUCTION

Otitis media is a very common childhood problem. Approximately 84% of children will experience one or more ear infections by the age of 3 years, and 46% will have two or more episodes.[1] Three bacteria, *Streptococcus pneumoniae*, nontypeable *Hemophilus influenzae*, and *Moraxella catarrhalis*, cause approximately 50% of the episodes, while 30% to 40% have no identifiable bacterial cause.[2] In recurrent and chronic forms of otitis media, nontypeable *H influenzae* assumes a more prominent role.[3-6] Thus, initial empiric treatment is most often directed against the three major pathogens. At the present time, ampicillin-amoxicillin is recommended as the primary drug for acute otitis media.[2] The purpose of the present study was to ascertain the effects of prior antibiotic treatment on the course of middle ear disease and on antibiotic susceptibility patterns.

MATERIALS AND METHODS

Population. Two hundred twenty children were enrolled in a prospective study of otitis media. The children ranged in age from birth to 3 years at the time of entrance into the study. Thirty-nine percent were at least 6 months old, 32% were 7 to 12 months old, and 29% were more than 12 months old. Thirty-two percent had no history of otitis media, 51% had one to five episodes, and 17% had more than five episodes at the time of entrance into the study. The children were examined regularly every 3 months and during episodes of otitis media. Otitis media with effusion was diagnosed by pneumatic otoscopy and tympanometry. Subjects were categorized at clinical presentation as symptomatic or asymptomatic. Symptomatic subjects exhibited fever, otalgia, upper respiratory tract signs, ear drainage, or a bulging eardrum, while asymptomatic individuals had evidence of middle ear fluid alone. The duration of middle ear fluid was classified as acute (less than 3 weeks), subacute (3 weeks to 3 months), and chronic (more than 3 months). The use of antibiotics within 30 days prior to the tympanocentesis was recorded as part of the epidemiologic data.

Isolation and Identification of Bacteria. A total of 320 tympanocenteses were performed for otitis media. Middle ear fluid was aspirated into an Alden-Senturia trap and transferred to the Bacteriology Laboratory. An aliquot of fluid was cultured aerobically on plates of 5% sheep blood, phenylethanol agar with 5% sheep blood, chocolate agar, and MacConkey agar, and in brain-heart infusion broth (Remel, Lenexa, Kan). The plates were incubated in 5% CO_2 at 37°C except for MacConkey agar and brain-heart infusion broth, which were incubated in a non-CO_2 incubator. Bacterial isolates were identified according to standard laboratory procedures.[7] Nontypeable *H influenzae* was characterized by X and V factors and by an absence of agglutination with typing sera. *Streptococcus pneumoniae* was identified by bile solubility. *Moraxella catarrhalis* was identified by the oxidase

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From the Division of Infectious Diseases (Faden, Ogra) and the Departments of Pediatrics (all authors) and Otolaryngology (Bernstein, Brodsky, Stanievich), State University of New York School of Medicine at Buffalo, and Children's Hospital of Buffalo (all authors), Buffalo, New York. This work was supported in part by a grant from the National Institutes of Health/National Institute of Child Health and Human Development (HD 19679).

REPRINTS — Howard Faden, MD, Division of Infectious Diseases, Children's Hospital of Buffalo, 219 Bryant St, Buffalo, NY 14222.

TABLE 1. CHARACTERISTICS OF CHILDREN AND EPISODES OF OTITIS MEDIA

Characteristics	Streptococcus pneumoniae	*Nontypeable* Hemophilus influenzae	Moraxella catarrhalis	*Total*
No. of episodes*	22	40	21	83
Age				
Range (y)	0.8-1.8	0.5-3.0	0.7-2.0	0.5-3.0
Mean ± SD (y)	1.3±0.4	1.5±0.8	1.2±0.4	1.4±0.6
Sex (M:F)	11:11	21:19	11:10	43:40
Episodes				
Range	1-11	1-13	1-10	1-13
Median	6	6	6	6
Symptoms				
Symptomatic	16	22	8	46
Asymptomatic	6	18	13	37
Duration				
Acute (<3 wk)	17	18	9	44
Subacute (3 wk to 3 mo)	1	11	3	15
Chronic (>3 mo)	4	11	9	24
Prior antibiotics				
Yes	7	22	16	45
No	15	18	5	38
Antibiotic used				
Ampicillin-amoxicillin	4	13	10	27
Cefaclor	2	6	1	9
Trimethoprim-sulfamethoxazole	1	3	3	7
Ampicillin-clavulanate	0	0	2	2

*Sixteen children had two or more episodes of otitis media, and each episode in individual was due to different pathogen.

reaction, colonial morphology, Gram stain, and quad Ferm (Api, Analytab Products, Plainview, NY). Aerobic cultures of the middle ear fluid yielded nontypeable *H influenzae* in 23%, *S pneumoniae* in 14%, *M catarrhalis* in 11%, and other organisms (coagulase-negative and -positive staphylococci, diphtheroids, viridans streptococci, group A *Streptococcus*, and *H influenzae* type b) in 30%. Twenty-seven percent of the effusions were sterile.

Antimicrobial Susceptibility Testing. Antimicrobial disk susceptibility tests were performed according to the recommendations of the National Committee for Clinical Laboratory Standards when applicable.[8,9] Briefly, bacterial colonies grown on agar plates for 18 to 24 hours were removed and suspended in saline to a turbidity equivalent to a barium sulfate McFarland standard of 0.5. The suspension was streaked with a swab over an entire agar surface. This was repeated several times after rotating the plate. After the excess moisture was absorbed, drug-impregnated disks were applied. The following disks were used: penicillin 10 μg, ampicillin 10 μg, and oxacillin 1 μg (Difco Laboratories, Inc, Detroit, Mich). Nontypeable *H influenzae* susceptibility testing was performed on Mueller-Hinton agar supplemented with 1% hemoglobin and 1% Isovitalex (BBL, Inc, Baltimore, Md); zones of inhibition were measured after 18 to 24 hours of incubation at 37°C in 5% CO_2. Ampicillin susceptibility of nontypeable *H influenzae* was defined by a zone of inhibition of 20 mm or more.[8] *Streptococcus pneumoniae* and *M catarrhalis* susceptibility testing was performed on Mueller-Hinton agar with sheep blood; zones of inhibition were measured after 18 to 24 hours of incubation at 37°C in a non-CO_2 incubator. Penicillin susceptibility of *S pneumoniae* was assessed with a 1-μg oxacillin disk.[10] Ampicillin susceptibility of *M catarrhalis* was defined by a zone of inhibition of 29 mm or more.[9,11]

Statistics. Data were analyzed by χ^2 with Fisher's exact test, and with Student's unpaired *t* test.

RESULTS

Population. Sixty-two children constituted the study population for the present report. They represented only those children who had otitis media due to *S pneumoniae*, nontypeable *H influenzae*, or *M catarrhalis* and who had sufficient clinical and laboratory data for analysis. Only one episode of otitis media due to the same type of pathogen in a single subject with recurrent infections was evaluated. Children with mixed infections were excluded. There were 31 boys and 31 girls who ranged between 6 months and 3 years of age. The individuals had experienced a prior history of otitis media of between 1 and 13 episodes (median, 6 episodes). During the 3-year period of observation included in this study, the subjects had 83 separate episodes of otitis media; 46 children had 1 episode, 11 had 2 episodes, and 5 had 3 episodes (Table 1). Forty-six of the episodes were categorized as symptomatic and 37 as asymptomatic. The infections were classified as acute in 44, subacute in 15, and chronic in 24.

TABLE 2. EFFECT OF PRIOR TREATMENT ON DEVELOPMENT OF AMPICILLIN RESISTANCE

Organism	*None*	*Ampicillin-Amoxicillin*	*Other*	*Total*
Streptococcus pneumoniae	0/15 (0%) a	0/4 (0%) b	0/3 (0%)	0/22 (0%)
Nontypeable *Hemophilus influenzae*	7/18 (39%) c	6/13 (46%) d	4/9 (44%)	17/40 (43%)
Moraxella catarrhalis	4/5 (80%) e	10/10 (100%) f	5/6 (83%)	19/21 (90%)
Total	11/38 (30%) g	16/27 (59%) h	9/18 (50%)	36/83 (43%)

a versus b, c versus d, and e versus f, not significant.
g versus h, $p<.025$.

Bacteriology and Penicillin-Ampicillin Susceptibility. Twenty-two episodes of otitis media were due to *S pneumoniae*, 40 episodes were due to nontypeable *H influenzae*, and 21 episodes were due to *M catarrhalis* (Table 1). Among the 16 children who had more than 1 episode of otitis media during the observation period, each episode in an individual was due to a different pathogen.

Streptococcus pneumoniae was fully susceptible to penicillin. In contrast, 42% of nontypeable *H influenzae* isolates were resistant to ampicillin. Ninety percent of strains of *M catarrhalis* were resistant to ampicillin.

Differences in Characteristics of Children by Pathogen. The three groups of children were similar with respect to age, sex, and number of episodes of otitis media. The majority of children with pneumococcal (73%) and *H influenzae* (55%) disease were symptomatic at the time of presentation, while only 38% of children with *M catarrhalis* were symptomatic ($p<.05$). More than 75% of children with pneumococcal disease had acute otitis media, compared to 42% or less of the children with *H influenzae* and *M catarrhalis* infections ($p<.01$).

Effect of Prior Antibiotic Treatment. Antibiotics had been administered in 45 of 83 episodes (54%) between 3 and 30 days prior to the tympanocentesis. Symptoms were present in 38% of the treated individuals and in 70% of the untreated ($p<.025$). Overall, ampicillin-amoxicillin resistance occurred more often among bacterial isolates from children previously treated (59%) than among isolates from untreated children (30%; $p<.025$; Table 2). However, no significant differences were detected for the individual pathogens.

Quantitative bacteriology was performed on 51 middle ear fluids. Children with acute otitis media tended to have a greater number of bacteria in middle ear fluids than children with subacute or chronic otitis media ($3.2 \times 10^4 \pm 12$ versus $7.9 \times 10^3 \pm 10$ bacteria per milliliter), but the difference was not statistically significant. Regardless of the pathogen, symptomatic children had significantly more bacteria per milliliter in middle ear fluids than asymptomatic children ($3.9 \times 10^4 \pm 12$ versus $6.3 \times 10^3 \pm 10$; $p=.05$; Fig 1). Twenty-seven of the specimens came from children who had not received antibiotics and 24 from children who had. Although 70% of middle ear fluids from untreated subjects contained more than 10^3 bacteria per milliliter and 54% of middle ear fluids from treated subjects contained more than 10^3 bacteria per milliliter, the mean ± SD bacterial counts for the two groups did not differ significantly ($2.0 \times 10^4 \pm 12$ versus $1.0 \times 10^4 \pm 10$; not significant). For individual pathogens, *S pneumoniae* ($4.0 \times 10^4 \pm 16$ per milliliter) and nontypeable *H influenzae* ($2.0 \times 10^4 \pm 16$ per milliliter) tended to have more bacteria than *M catarrhalis* ($7.9 \times 10^3 \pm 2$) among untreated subjects (Fig 2). Prior treatment appeared to reduce the colony count most dramatically for *S pneumoniae* (90%), but the difference was not statistically significant.

DISCUSSION

The population in the present study primarily represented a group of children with recurrent episodes of otitis media. As expected, nontypeable *H influenzae* accounted for the greatest proportion of the cases.[3-6] Children with nontypeable *H influenzae* and *S pneumoniae* were more often symptomatic than were children with *M catarrhalis*. This may have been due, in part, to the greater number of bacteria contained in middle ear fluids

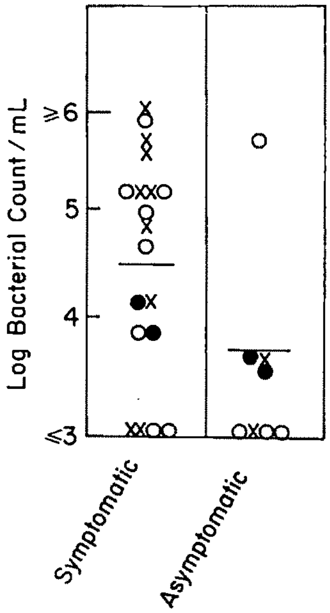

Fig 1. Comparison of bacterial counts in middle ear fluids from untreated symptomatic and asymptomatic children with otitis media. Difference between mean bacterial count of symptomatic and asymptomatic children was significant at $p=.05$. X — *S pneumoniae*, O — nontypeable *H influenzae*, ● — *M catarrhalis*.

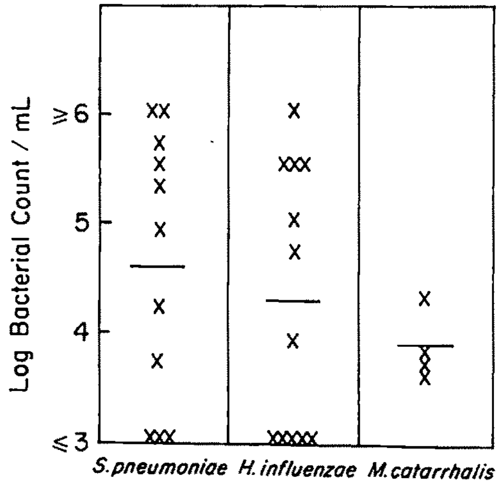

Fig 2. Comparison of bacterial counts in middle ear fluids infected with *S pneumoniae*, nontypeable *H influenzae*, or *M catarrhalis* (untreated subjects).

with the former two organisms. A similar disparity of colony counts in middle ear fluids was observed previously by Wald et al.[12] Further analysis of bacterial counts in middle ear fluids suggested that acute episodes of ear infection tended to have more bacteria than subacute or chronic episodes, although the difference was not significant.

Prior use of antibiotics was associated with a reduction in symptoms at the time of presentation for the tympanocentesis. Although the number of bacteria in middle ear fluids was not statistically less in children previously treated, circumstantial evidence suggested that the decline in symptoms was related, in part, to lower bacterial counts in middle ear fluids.

Prior use of antibiotics was also associated with a change in the pattern of antibiotic susceptibilities. Overall, 42% of the strains of nontypeable *H influenzae* were resistant to ampicillin-amoxicillin. Since nontypeable *H influenzae* resistance to ampicillin was first identified in 1976, there has been a progressive rise in the resistance rate.[13] In Pittsburgh alone, resistance doubled from 17% in 1981 to 34% in 1986.[2] Ampicillin resistance rates, however, appear to vary markedly among medical centers in various regions. For example, in a recent national survey with 2,811 nontypeable *H influenzae* isolates from 30 medical centers, resistance to ampicillin varied from 0% to 29%.[14] Similarly, *M catarrhalis* demonstrated a high rate of ampicillin resistance (90%) in the present report. Even if a smaller zone of inhibition (19 mm) had been used to define resistance, the rate of resistance would have exceeded 75%.[15] On the other hand, *S pneumoniae* was uniformly susceptible to the antibiotics tested. Although others have reported a number of penicillin-resistant or intermediately susceptible strains, all of the isolates examined in this study were fully susceptible to penicillin.[16,17] The failure to detect resistance among isolates of pneumococci within a population with recurrent otitis media is perplexing in light of recent reports of resistance from the United States and other countries.[18]

In conclusion, the present study demonstrates that prior treatment with antibiotics dramatically alters the clinical picture of otitis media and results in an increase in antibiotic resistance among middle ear pathogens such as nontypeable *H influenzae* and *M catarrhalis*, but not *S pneumoniae*.

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DIAGNOSTIC AND OPERATIVE SINUS ENDOSCOPY

A course on Diagnostic and Operative Sinus Endoscopy will be held January 24-25, 1992, at the NYU Medical Center, Schwartz Lecture Hall, in New York. For further information, contact NYU Medical Center, Post-Graduate Medical School, 550 First Avenue, New York, NY 10016; (212) 263-5295.

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INTERNATIONAL HEARING AID CONFERENCE
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An International Hearing Aid Conference will be held June 15-17, 1993, at The University of Iowa, Iowa City, Iowa. For information on registration and accommodation, contact the Conference Center, University of Iowa, Memorial Union, Iowa City, IA 52242; (319) 335-3231, Fax (319) 335-3407. For information on Call for Papers, contact Regina Tisor (319) 356-2471, Fax (319) 356-4547. We have applied for Continuing Education Units from ASHA and HAIC.

Ann Otol Rhinol Laryngol 101:1992

PLASMA CELL GRANULOMA OF THE MIDDLE EAR AND MASTOID

CASE REPORT

NICK C. BENTON, MD
PANORAMA CITY, CALIFORNIA

HAROLD W. KOROL, MD
REDWOOD CITY, CALIFORNIA

LAWRENCE T. SMYTH, JR, MD
REDWOOD CITY, CALIFORNIA

We present the case of a 37-year-old man with plasma cell granuloma affecting the middle ear and mastoid. At magnetic resonance imaging scan, the lesion appeared as a homogeneously enhancing mass of soft tissue replacing the majority of the mastoid bone and causing vascular compression. After surgical resection, microscopic examination showed predominantly plasmacytes, and histochemical studies confirmed a polyclonal origin consistent with nonneoplastic plasma cell granuloma. We believe this is the first case report of plasma cell granuloma affecting the middle ear and mastoid.

KEY WORDS — mastoid, middle ear, plasma cell granuloma.

INTRODUCTION

Plasma cell granuloma is a rare lesion formed by proliferation of polyclonal, nonneoplastic plasma cells. Several case reports in the literature describe plasma cell granuloma of the brain,[1-3] lungs,[4] gastrointestinal tract,[5] kidneys,[6] salivary glands, and skin.[7] However, no cases of middle ear or mastoid plasma cell granuloma have yet been reported. We present an unusual case confirmed by histologic and histochemical studies.

CASE REPORT

At 27 years of age the patient had a chronic, draining oro-antral fistula after a tooth extraction. The fistula was closed and the Caldwell-Luc opertion was done at another institution. Tissue was removed from the maxillary sinus, and the lesion was diagnosed as atypical histiocytosis X. Results of metastatic evaluation were negative for disseminated histiocytosis X.

The patient had been unavailable for follow-up

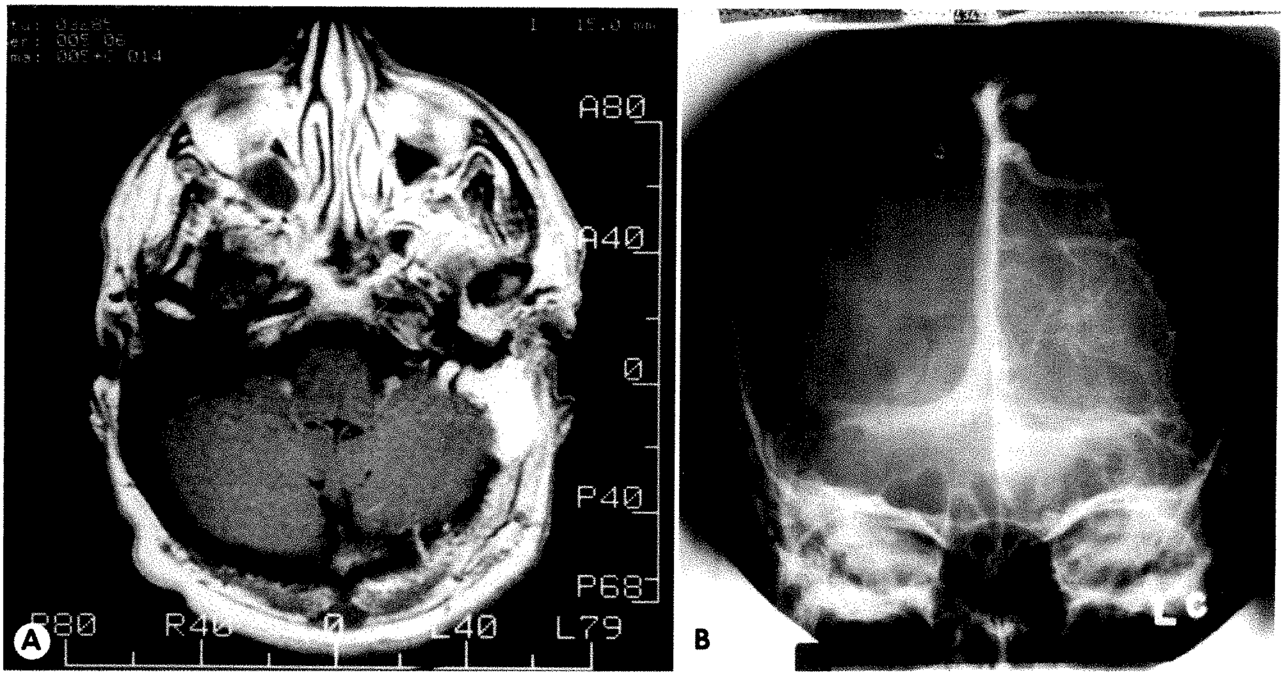

Fig 1. Left mastoid bone lesion. A) Magnetic resonance image, axial view, enhanced on T1-weighted image. B) Venous phase angiogram. Frontal view shows how left major venous drainage pathways have failed to enhance.

From the Departments of Otolaryngology–Head and Neck Surgery (Benton, Korol) and Pathology (Smyth), Kaiser Permanente Medical Center, Redwood City, California.

Presented at the meeting of the Pacific Coast Oto-Ophthalmological Society, Vancouver, British Columbia, June 18-23, 1990.

REPRINTS — Nick C. Benton, MD, Southern California Permanente Medical Group, 13652 Cantara St, Panorama City, CA 91402.

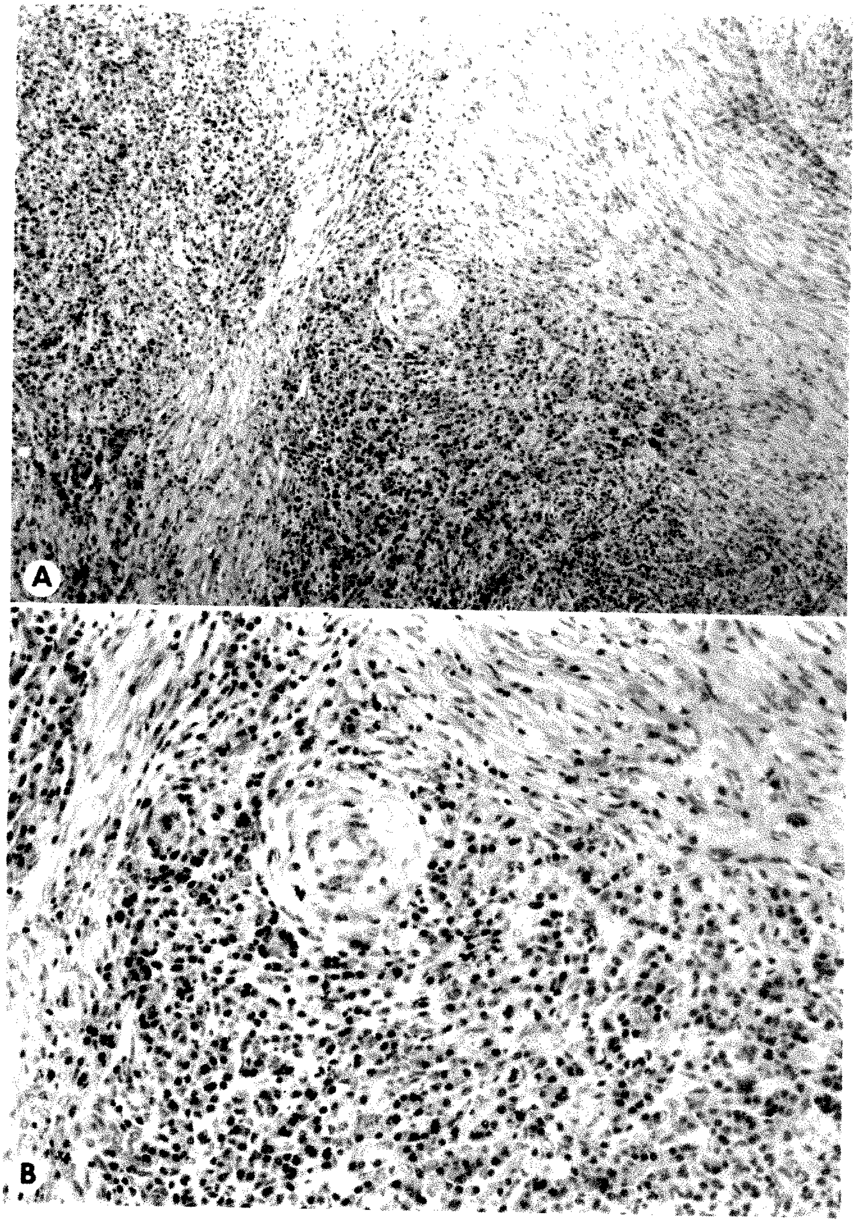

Fig 2. Photomicrographs of histologic specimen showing predominance of plasmacytes and absence of meningothelial cells. A) Low-power view. B) High-power view.

at that facility for 10 years when he was seen in our medical office for left ear pain and diminished hearing that had persisted for nearly 2 years. The patient denied having ear drainage, tinnitus, vertigo, or other cranial nerve symptoms. At physical examination, the tympanic membrane was normal and mobile. Cranial nerve examination results were normal. An audiogram showed a diminished speech reception threshold with a moderate to severe conductive loss and diminished speech discrimination. A magnetic resonance imaging (MRI) scan (Fig 1A) showed a homogeneously enhancing soft tissue mass in the left mastoid bone that extended into the middle cranial fossa and petrous apex. We believed that this mass was consistent with a primary meningioma of the temporal bone. Because vascular compression was evident at MRI, arteriography was done, which confirmed occlusion of the distal left transverse and sigmoid sinuses (Fig 1B).

The patient was taken to the operating room, where he had a left temporo-occipital craniotomy with radical mastoidectomy and obliteration of the middle ear. Findings at operation showed a tan-red soft tissue mass completely filling the mastoid antrum and eroding the incus and head of the malleus. The stapes footplate was intact, and the superstructure was absent. The facial nerve was widely dehiscent in the mastoid, and the mass extended directly to both the middle and posterior cranial fossae. All identifiable tumor was removed during the operation.

The postoperative course was uneventful. The patient had no cranial nerve injury or worsened sensorineural hearing loss as a result of the operation.

Pathology. Microscopic examination revealed a fibrotic and lymphoplasmacytic infiltrate without identifiable meningothelial cells (Fig 2). Histochemical stains confirmed polyclonal origin and both lambda and kappa light chains. A final diagnosis of an inflammatory pseudotumor, a plasma cell variant, was made. The description of specimens from the Caldwell-Luc operation done 10 years earlier was identical, although direct comparison was not possible.

DISCUSSION

We have described the case of a plasma cell granuloma that had first appeared 10 years earlier affecting the maxillary sinus. Mirra et al[8] described an 11-year-old girl who had an inflammatory mass with predominant plasma cell infiltrates in the anterior cranial fossa and in whom, during postoperative follow-up, a maxillary sinus lesion developed. The interval between the clinical appearance of the two lesions, however, was only 13 months. These two cases and the histologic pictures are similar. However, the comparison may not be valid because the meningothelial elements present in the case reported by Mirra et al indicate a meningioma variant and not a true plasma cell granuloma. Sinus histiocytosis with massive lymphadenopathy, another disorder that has been described, may intracranially mimic a meningioma,[9] and a link between sinus histiocytosis and plasma cell granuloma has been suggested.[8]

Central nervous system disease has been treated surgically; two patients received postoperative radiotherapy.[1,3] Horten et al[10] reported three cases of meningiomas with conspicuous plasma cell lymphocytic components. One patient died of persistent disease after surgical resection with postoperative irradiation and chemotherapy. However, it is unclear if these atypical meningiomas would have responded to treatment in the same way as a true plasma cell granuloma. With this exception, the patients followed up in these reports remained free of disease, but long-term follow-up was not noted. Our patient received postoperative radiotherapy and remained free of disease for 1 year after operation, as shown by subsequent MRI scans and examination results.

SUMMARY

We believe that this is the first reported case of plasma cell granuloma involving the middle ear and mastoid. The presence of an identical lesion of the maxillary sinus 10 years earlier attests to the indolent progression of this disorder. Long-term follow-up is advised for patients with a diagnosis of plasma cell granuloma. Treatment has been primarily surgical. Postoperative radiotherapy has been used in our patient and in two other reported patients with central nervous system disease.[1,3] Short-term prognosis has been good, but long-term results are unavailable.

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EFFECTS OF AEROSOLIZED DEXAMETHASONE ON ACUTE SUBGLOTTIC INJURY

THOMAS C. KRYZER, JR, MD
CHARLOTTESVILLE, VIRGINIA

CARLOS GONZALEZ, MD
HATO REY, PUERTO RICO

MAJ LAWRENCE P. A. BURGESS, MC, USA
HONOLULU, HAWAII

Aerosolized dexamethasone was used in a two-phase study to determine the possible effects on acute subglottic injury in the ferret animal model. In phase 1, equivalent subglottic injuries were made in 10 animals by using the brush technique, and the animals were divided into two groups. The treatment group received aerosolized dexamethasone at 2, 4, and 6 hours postinjury. All animals were examined 2, 4, 6, and 24 hours after the injury. The clinical condition of each animal was evaluated and their airways were measured. The animals were then painlessly killed and the larynges were frozen, sectioned, and photographed at 1-mm intervals. A computer-linked digitizer pad was used to measure the subglottic dimensions. The results show a trend for the treated animals to have a larger subglottic airway as compared to the untreated (control) group. The phase 1 study suggests that there may be an improvement in the subglottic airway when treated acutely with aerosolized dexamethasone. In phase 2, 20 additional animals were studied by using the same methods of injury and treatment as in phase 1. The subglottic airways of these animals were evaluated with histomorphometric analysis on fixed histologic sections. A statistically significant difference was found between the subglottic airways of the treated and untreated animals favoring treatment with aerosolized dexamethasone. Aerosolized dexamethasone appears to be beneficial in preserving the subglottic airway after injury, possibly secondary to decreasing the edema associated with injury.

KEY WORDS — animal model, laryngeal injury, steroid treatment.

INTRODUCTION

Acute subglottic injury with subsequent edema may cause significant airway narrowing, manifested by severe compromise of ventilation and oxygenation. Causes of airway obstruction include infectious, traumatic, and inflammatory diseases; however, a significant contributing factor in all causes is acute edema with subsequent airway compromise.[1]

Subglottic trauma is frequently encountered in the form of intubation injury and laryngotracheobronchitis, presenting with symptoms of stridor, retractions, and a "croupy" cough. Children are most susceptible to this problem, with postintubation croup being rather uncommon in the adult. Subglottic mucosal injury with subsequent edema is the purported cause of this disorder.[1] The amount of injury may vary in severity from mild edema of the subglottic soft tissues to frank mucosal ulceration. Prolonged intubation as well as traumatic intubation has been implicated in significant subglottic injury. Positive pressure ventilation causing endotracheal tube movement in the subglottis and repeated trauma to this tissue may lead to further mucosal injury. The subglottic region is at particular risk to effects of injury, since it is the narrowest portion of the airway and is formed by a complete cartilaginous ring. Significant injury to this area with subsequent edema causes airway compromise and delays successful extubation. Reintubation, while relieving the obstruction, causes additional trauma to an already injured area. Tracheotomy, if required, is associated with other significant airway morbidities.

Chronic subglottic stenosis as a long-term complication of acute laryngeal injury occurs in only a small percentage of children.[1] However, this is a devastating complication and has caused investigators to pursue medical management and prophylaxis such as parenteral and intralesional steroids.[2-5] Although these studies have shown possible beneficial effects in the acute phase of edema, both of these treatments have their own significant drawbacks and side effects. Possible systemic effects of parenteral steroids and repeated general anesthesia for the delivery of intralesional steroids are associated with these two modes of treatment. Aerosolized steroids, if effective, would possess the benefits of a noninvasive delivery technique with negligible systemic absorption.

In order to study the possible effects of aerosolized dexamethasone on the edema associated with acute subglottic injury, we performed a study using the

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From the Departments of Surgery (all authors) and Pediatrics (Gonzalez), Uniformed Services University of the Health Sciences, and the Otolaryngology–Head and Neck Surgery Service, Walter Reed Medical Center (Kryzer, Burgess), Washington, DC. Supported in part by Uniformed Services University of the Health Sciences grant R090AF-01. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Army or the Department of Defense. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee of the Uniformed Services University of the Health Sciences.

Presented in part at the meeting of the American Society of Pediatric Otolaryngology, San Diego, California, May 19, 1989.

REPRINTS — Thomas C. Kryzer, Jr, MD, Dept of Otolaryngology–Head and Neck Surgery, University of Virginia Health Sciences Center, Box 430, Charlottesville, VA 22908.

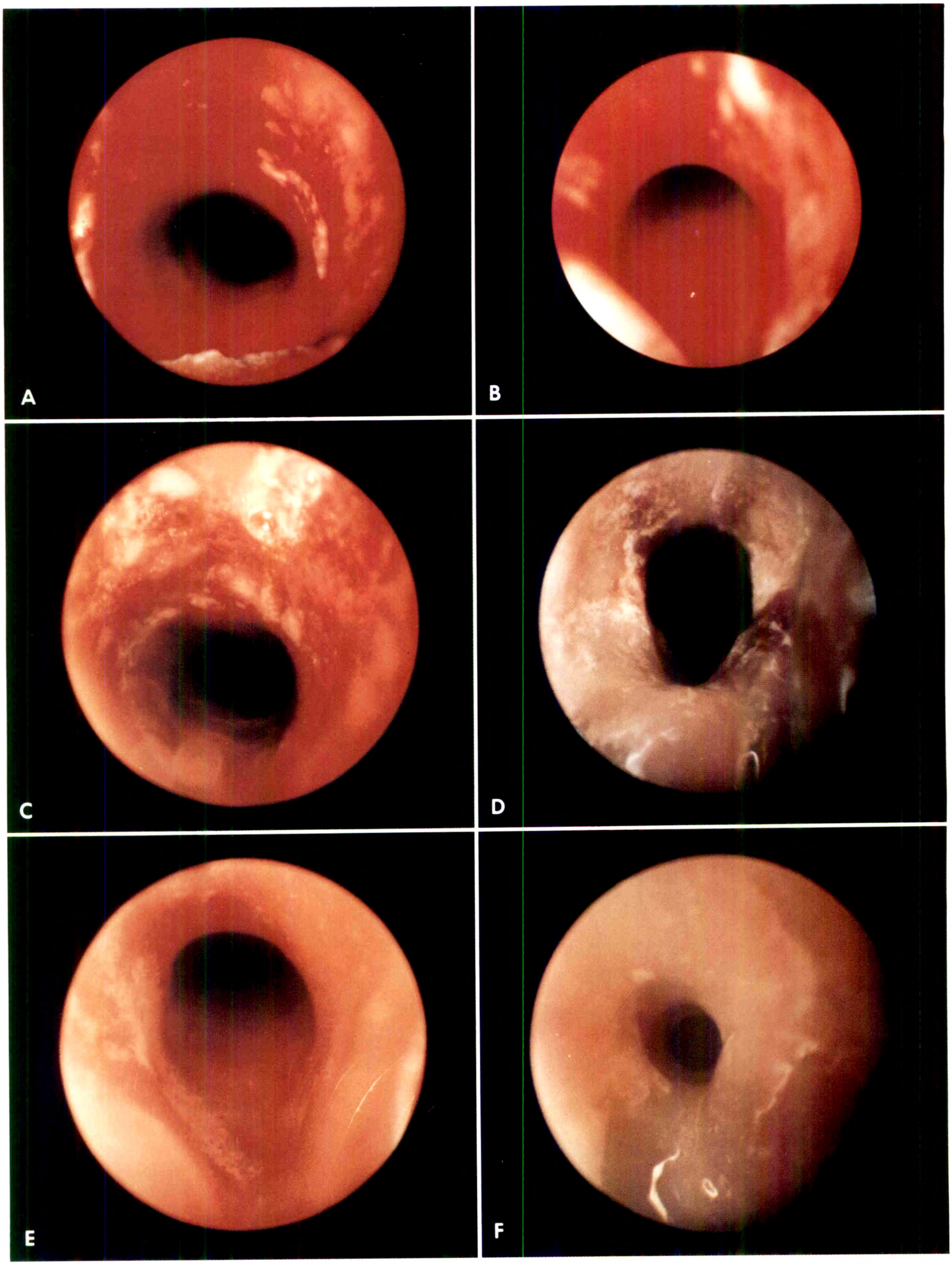

Fig 1. Endoscopic views of larynx. A) Two hours after injury in treated animal. B) Two hours after injury in untreated animal. C) Six hours after injury in treated animal. D) Six hours after injury in untreated animal. E) Twenty-four hours after injury in treated animal. F) Twenty-four hours after injury in untreated animal.

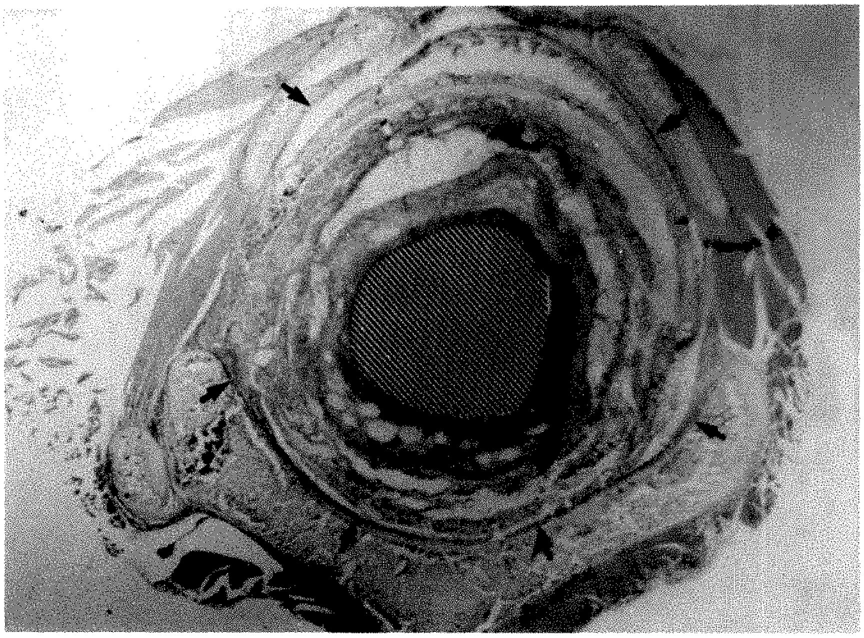

Fig 2. Histologic section of ferret larynx through subglottis (H & E, original x6.25). Cross-hatching — subglottic airway, arrows — intracricoid area.

ferret animal model of brush intubation injury as described by Woods et al.[2] Ferrets were selected because their larynges closely approximate the size of the pediatric larynx and they are reliable animals for laboratory study. The specific aims of the study were to 1) assess possible effects of aerosolized steroid on subglottic airway size following acute subglottic injury and 2) confirm the ferret animal model as a reliable model for acute subglottic injury. The investigation was conducted in two phases and the results of both phases are reported.

MATERIALS AND METHODS

Phase 1. Ten 10-week-old ferrets were given ketamine hydrochloride anesthesia. Subglottic injuries were made by inserting a 9-mm nylon test tube brush in the subglottic space and rotating the brush 360° in a clockwise direction, then 360° in a counterclockwise direction. Following the injury, six animals were randomly placed into a treatment group and four animals were placed in a nontreatment (control) group. The treatment group received 8 mg/kg of dexamethasone aerosolized in an inhalation chamber at 2, 4, and 6 hours postinjury. Control animals spent an equal amount of time in a high-humidity chamber. Both groups were maintained in a high-humidity environment throughout the entire study. All animals were examined and the presence or absence of stridor and retractions was noted at 2, 4, 6, and 24 hours after the injury. During each examination the airway of each animal was measured by recording the largest endotracheal tube (ie, 2.5, 3.0, or 3.5 mm outside diameter) that could be placed in the airway and still yield an air leak of less than 35 cm H_2O. The animals were painlessly killed at 24 hours and the larynges were harvested.

The larynges were fixed in 10% formalin and later frozen in methylcellulose with hexane and dry ice. The blocks containing the frozen larynges were then cut on a frozen section microtome at 50-μm intervals. Every 20th section was photographed to obtain 1-mm intervals between photographs throughout the entire larynx of each study animal. The subglottic region was determined from the photographs as that area that had a visible and complete or nearly complete cricoid ring. Three representative photographs of the subglottic region were then selected from each animal and projected images were examined by using a calibrated computer-linked digitizer pad. The digitizer pad was used to measure the 1) minimum subglottic airway and 2) the intracricoid transverse dimension. All measurements were made at the narrowest portion of the subglottic airway for each animal. The transverse dimension between the cricoid laminae (intracricoid distance) was used in order to assess any inherent size differences in the subglottic airways of the animals. The minimum subglottic area was used to express the smallest subglottic airway, in square millimeters, for each animal.

Phase 2. Subglottic injuries were produced in a manner identical to that of phase 1 in an additional 20 animals. They were then randomized into treatment and nontreatment (control) groups. The treatment and nontreatment groups received the same treatment as in phase 1 of the study. The larynges were photographed preinjury and postinjury with a Storz-Hopkins 2715 0° quartz rod telescope and an Olympus OM-2 35-mm SLR camera. After the injuries had been produced the animals were photographed at 2, 4, 6, and 24 hours (Fig 1). At 24 hours the animals were painlessly killed and the larynges were harvested, fixed in formalin, cut in 5-μm sections, and processed for hematoxylin and eosin staining. The subglottic region was identified in

AIRWAY DATA (PHASE 2)

	Treated Mean (mm^2)	*Untreated Mean (mm^2)*	*Standard Error of Mean*	*p*
Subglottic airway	10.1	7.6	0.78	.032
Intracricoid area	22.3	19.8	1.39	>.22

each animal by the presence of a complete or nearly complete cricoid cartilage ring. Three sections from the narrowest portion of the subglottis were selected from each animal. Each histologic section of the subglottis was measured for 1) subglottic airway area and 2) the total area bounded by the cricoid cartilage (Fig 2). The subglottic area was measured directly from the histologic sections of the subglottis by means of histomorphometric analysis as described by J. O. Hollinger and J. P. Schmitz (unpublished observations, 1986) using hardware and software developed by Cambridge Instruments.

Statistical analysis using standard deviation, standard error of the mean, and Student's *t* test was performed.

RESULTS

All animals survived both phases of the study. Specimens from two animals in the treatment group of phase 1 and one in each group (treated and untreated) in phase 2 were damaged during processing. This left four animals in each group in the phase 1 study and nine animals in each group in the phase 2 study. Because two different measurement techniques were used in phases 1 and 2, a composite analysis was not performed.

Clinical observation showed that one of six treated animals in the phase 1 study developed stridor or retractions whereas all of the untreated animals developed stridor and retractions by the end of the study. Airway measurements of the larynges studied in the phase 1 study consisted of 1) minimum subglottic airway area in square millimeters and 2) the intracricoid transverse dimension. The mean intracricoid transverse dimension was 5.29 mm for the treated group and 5.40 mm for the untreated group. The *t* statistic yields a p value of .384 indicating no statistical pretreatment difference between the two groups. Measurements on the minimum subglottic airway gave a mean for the treated group of 9.04 mm^2 and for the untreated group of 5.93 mm^2 ($p = .20$).

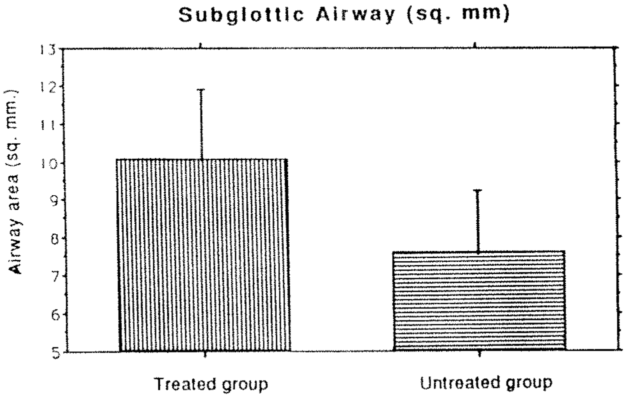

Fig 3. Minimum subglottic airway area in square millimeters. Error bars — + 2 SD.

In the phase 2 study 4 of 10 treated animals had stridor, while 9 of 10 of the untreated animals had stridor at the end of the study. Although preinjury and initial postinjury photographs were noted to be similar, after 6 hours there was a marked difference between the treated and untreated groups (Fig 1). Measurements on the larynges in phase 2 were 1) direct measurements of the subglottic airway from histologic sections and 2) the total subglottic area bounded by the cricoid cartilage (see Table and Fig 3). The mean subglottic airway area of the treated group was 10.1 mm^2, compared to the untreated group mean of 7.6 mm^2, giving a p value of .032. When the total intracricoid intercartilaginous space was measured, the p value was greater than .22, indicating no evidence of pretreatment bias between the groups.

DISCUSSION

Many methods for the treatment and prevention of subglottic edema following intubation have been described. This diversity of treatment methods indicates that no single treatment is clearly superior. Parenteral steroids, intralesional steroids, parenteral antibiotics, and topical antibiotics have all been used with some degree of success.[2-5] Edema of the submucosa in response to injury may lead to mucosal ischemia, ulceration, sloughing of mucosa, secondary infection, and chondritis. Eventual subepithelial fibrosis with granulation tissue leading to mature scar formation may progress to chronic subglottic stenosis.[6] Steroids are known to cause a decrease in the acute inflammatory phase of injury as well as in later fibroblastic proliferation in healing wounds.[7,8]

Previous clinical reports[1,3,4] have indicated that the maximal edema from intubation occurs at 1 to 2 hours. Ferret models show maximal edema within 24 hours.[2] Animal studies have shown that steroid therapy needs to be instituted early in the course of the inflammatory process to be beneficial.[4,5] Steroids inhibit the influx of inflammatory cells and limit capillary endothelial permeability. Steroid therapy therefore attempts to decrease or prevent submucosal fibrosis by reducing the inflammatory response in tissue injury.[6,7] These properties of steroids have led to their use in cases of laryngeal mucosal injury.

Our ferret model shows a statistically significant difference in the size of the subglottic airway between the treated and untreated groups with the use of aerosolized dexamethasone after subglottic injury. The untreated group showed clinical signs of more severe subglottic compromise, the development of stridor, and retractions in nearly all animals (4 of 4 in phase 1 and 9 of 10 in phase 2).

Airway measurements revealed a mean subglottic airway area 25% smaller in the untreated group, which corresponds to a radius difference of about 15%. By using Poiseuille's equation for the resistance to flow of a gas, $R = 8\ nl/\pi r^4$, when comparing the two groups, the untreated animals are predicted to have a resistance to airflow about 170% greater than the treated group secondary to the change in radius. The predicted increase in the resistance is a consequence of the radius-cubed factor in the denominator of the equation. This increased resistance to airflow is most likely responsible for the more severe clinical symptoms noted in the untreated animals. It is noteworthy that the airway measurements were made 18 hours after the treated group had received their last dose of steroid. The airway size differences might have been greater if the treated group had received additional steroid therapy beyond 6 hours after the injury.

CONCLUSION

The effects of aerosolized dexamethasone on the edema of acute laryngeal injury in the ferret model was studied in two phases. This study shows that aerosolized dexamethasone preserves the subglottic airway area and decreases the clinical severity of airway obstruction in the acutely injured ferret larynx. The observed differences between the airways of the two groups are associated with an increase of the predicted airway resistance of about 170% in the untreated animals. These results may have clinical implications in the treatment of subglottic injury in children by reducing the acute phase edema and thus preventing the need for prolonged intubation or tracheotomy.

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IMAGING CASE STUDY OF THE MONTH

FIBROUS DYSPLASIA OF THE SPHENOID SINUS

DONALD P. MUELLER, MD
KENNETH D. DOLAN, MD
WILLIAM T. C. YUH, MD
IOWA CITY, IOWA

CASE REPORT

A 31-year-old man with a history of recent onset of seizures, controlled by Tegretol, was evaluated by cerebral magnetic resonance imaging (MRI). Axial images were obtained. The dominant finding was in the left sphenoid sinus and greater wing. Proton density (TR 2,400/TE 20) images demonstrated low signal in the left sphenoid sinus with extension into the adjacent left middle cranial fossa. Some inhomogeneity was seen. The dominant pattern was decreased signal compared to that of bone marrow. With increased T2 weighting (TR 2,400/TE 70) the signal remained low compared to that of adjacent brain. No meningeal enhancement was identified following gadolinium administration (Fig 1).

Enhanced computed tomography was then performed. Predominately sclerotic change with thickening of bone in the left sphenoid sinus and adjacent proximal pterygoid and greater sphenoid wing was seen. This corresponded to the MRI signal abnormality (Fig 2).

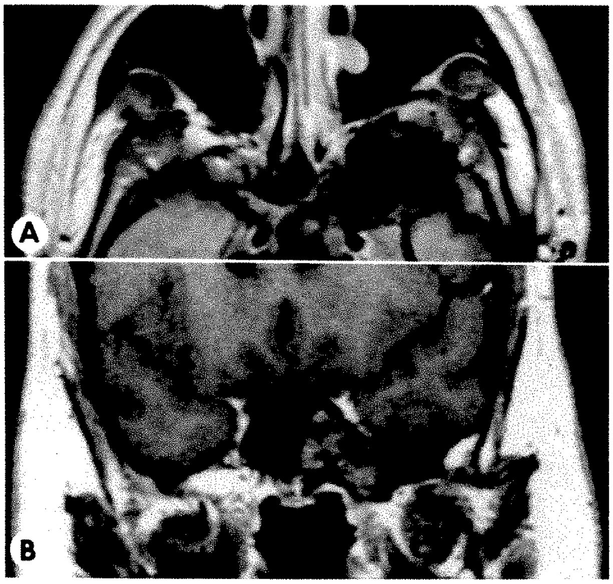

Fig 1. Magnetic resonance images of skull base. A) Axial T2-weighted, showing signal loss and expansion of left sphenoid greater wing. B) Coronal, contrast-enhanced T1-weighted, showing abnormal signal in left sphenoid sinus.

Radiographically the pattern was consistent with fibrous dysplasia. Neurologic and neurosurgical consultations were obtained. The consensus was that the patient was asymptomatic with respect to the osseous change. No further therapy or diagnostic procedure was deemed warranted.

DISCUSSION

Magnetic resonance imaging is based on hydrogen atom resonance. The primary source of signal is fat or water. Both the quantity of atoms and their local environment affect the signal. In general, inflammatory sinus lesions demonstrate increased signal on T2-weighted images. A low T2 signal indicates decreased water content. Within the sinuses, a loss of T2 signal indicates either an aggressive lesion such as a neoplasm or dried secretions.[1]

Fibrous dysplasia is a disorder of unknown origin in which normal bone is replaced by fibrous tissue

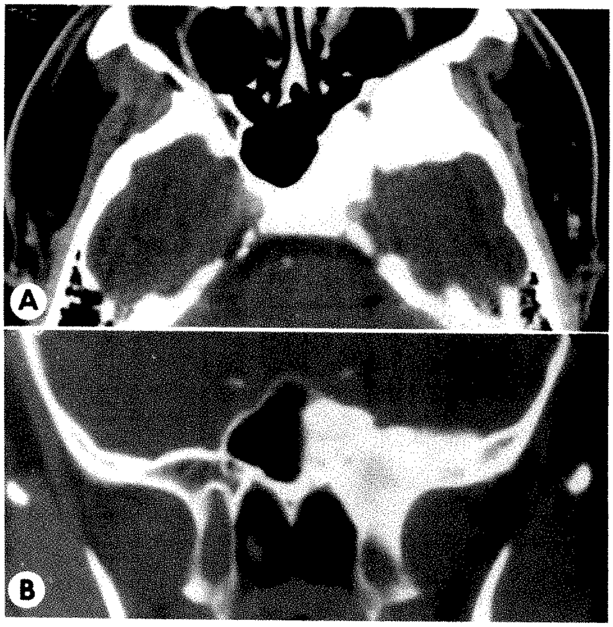

Fig 2. Computed tomograms of skull base. A) Axial, showing sclerosis and expansion of left sphenoid greater wing. B) Coronal, showing sclerosis of left sphenoid sinus and sclerosis and expansion of proximal pterygoid and greater wing.

From the Department of Radiology, The University of Iowa College of Medicine, Iowa City, Iowa.
REPRINTS — Donald P. Mueller, MD, Dept of Radiology, The University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

and poorly formed woven bone.[2] Leeds and Seaman[3] identified the frontal and sphenoid bones as the most common sites of calvaria involvement. Symptoms relate to bony overgrowth. Proptosis, foraminal compression, and deafness all may occur.[3]

Three plain film radiographic patterns have been described. Homogeneous density is seen in the sclerotic pattern. Relative lucency that frequently has dense margins is identified in the cystlike pattern. The pagetoid form is a mixed lesion with alternate areas of relative density and lucency. Varying proportions of radiolucent fibrous tissue and radiodense bone account for the spectrum of plain film patterns.[4]

A spectrum of MRI signal characteristics has also been reported. The signal on T1-weighted images is consistently decreased, with an intensity similar to that of skeletal muscle. The T2 signal, however, is variable. The signal may be brighter than, similar to, or less than that of subcutaneous fat.[5] It is assumed that the signal changes relate to the varying histology of the lesion.

In summary, our case demonstrated T2 signal loss within the sphenoid sinus with extension into the adjacent middle cranial fossa. Computed tomography confirmed that predominately sclerotic bony thickening was the source of the decreased signal. Enhanced MRI failed to demonstrate an adjacent meningioma as a source for hyperostosis. The lesion was therefore considered to be radiographically characteristic of fibrous dysplasia.

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PATHOLOGY CONSULTATION

"ADENOCARCINOMA, NOT OTHERWISE SPECIFIED": A DIMINISHING GROUP OF SALIVARY CARCINOMAS

JOHN G. BATSAKIS, MD
ADEL K. EL-NAGGAR, MD, PHD
MARIO A. LUNA, MD
HOUSTON, TEXAS

As refinements in classification with clinicopathologic correlations proceed, the "adenocarcinomas, not otherwise specified" (NOS) of salivary tissue are reduced in number. Clinicopathologic entities such as salivary duct carcinoma, terminal duct carcinoma, and epimyoepithelial carcinoma, formerly in the NOS category, are examples of this process. There remain, however, adenocarcinomas of salivary tissues that cannot be accommodated in conventional classifications. They are the least common of salivary carcinomas and manifest a cytoarchitecture ranging from a well-differentiated, low-grade appearance to high-grade, invasive lesions. This report addresses this group of carcinomas for which the NOS designation is still applicable.

Since carcinomas of salivary tissues take origin from the salivary duct unit, they are all generically "adenocarcinomas." The requirements of modern practice, however, dictate that clinicopathologic entities be recognized and classified; adenoid cystic, acinic cell, and mucoepidermoid carcinomas are just three examples of this recognition/classification process. There remains a heterogeneous group of gland-forming carcinomas of salivary origin that have been collectively embraced by the term "adenocarcinoma, not otherwise specified" (NOS).

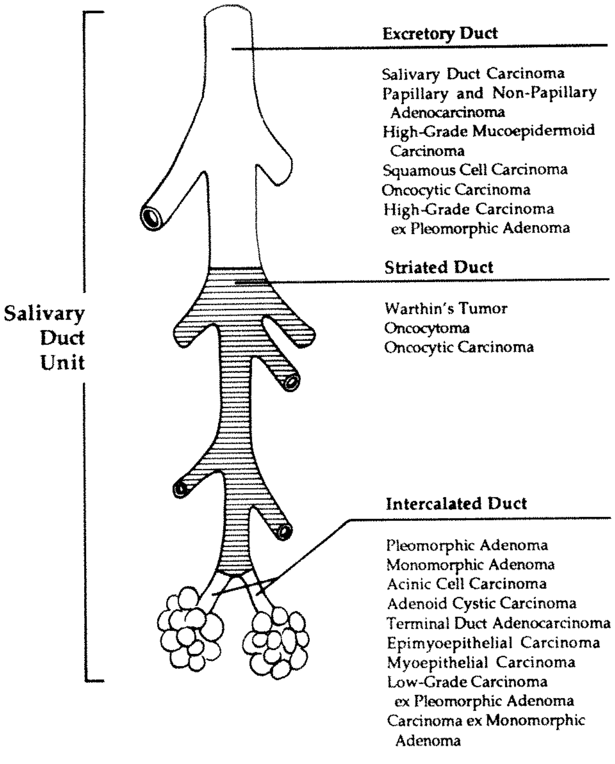

Fig 1. Salivary duct unit, generative unit for all salivary gland neoplasms, with its subdivisions and their types of neoplasms.

Over the past decade and a half, following an appreciation that there exists a wide range of biologic behavior within the NOS category, clinically pertinent and classifiable subsets have been defined.[1-4] In general, the biologic aggressiveness of these carcinomas follows their segregation according to the place of origin along the salivary duct unit (Fig 1).[5] Thus, terminal duct adenocarcinomas are characteristically low grade, salivary duct carcinomas are high grade, and epimyoepithelial carcinomas are intermediate in their clinical course.[1,2,4]

Residual within the adenocarcinoma NOS group after removal of the aforestated carcinomas are adenocarcinomas for which the literature is either scant or unclear because it includes too diverse a collection of carcinomas in its assessments.[6-8] The mucus-producing adenopapillary (nonepidermoid) carcinoma described by Blanck et al[9] is a case in point. It is defined by the authors as a collective term for a type of adenocarcinoma characterized by two main histologic features — mucous *and* papillary structures — and Blanck et al[9] required only one of the features to be included in their series. In the event, as judged by the photomicrographs accompanying the text of their report, acinic cell carcinomas, mucoepidermoid carcinomas, epimyoepithelial carcinomas, and ductal carcinomas were included under

SALIVARY DUCT CARCINOMA

No. of cases	58
Male to female ratio	5:1
Local recurrence or persistence (%)	39
Metastases to lymph nodes (%)	60
Distant metastases (%)	57
Mortality by 29 mo (%)	55

Data from Brandwein et al.[4]

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.
REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

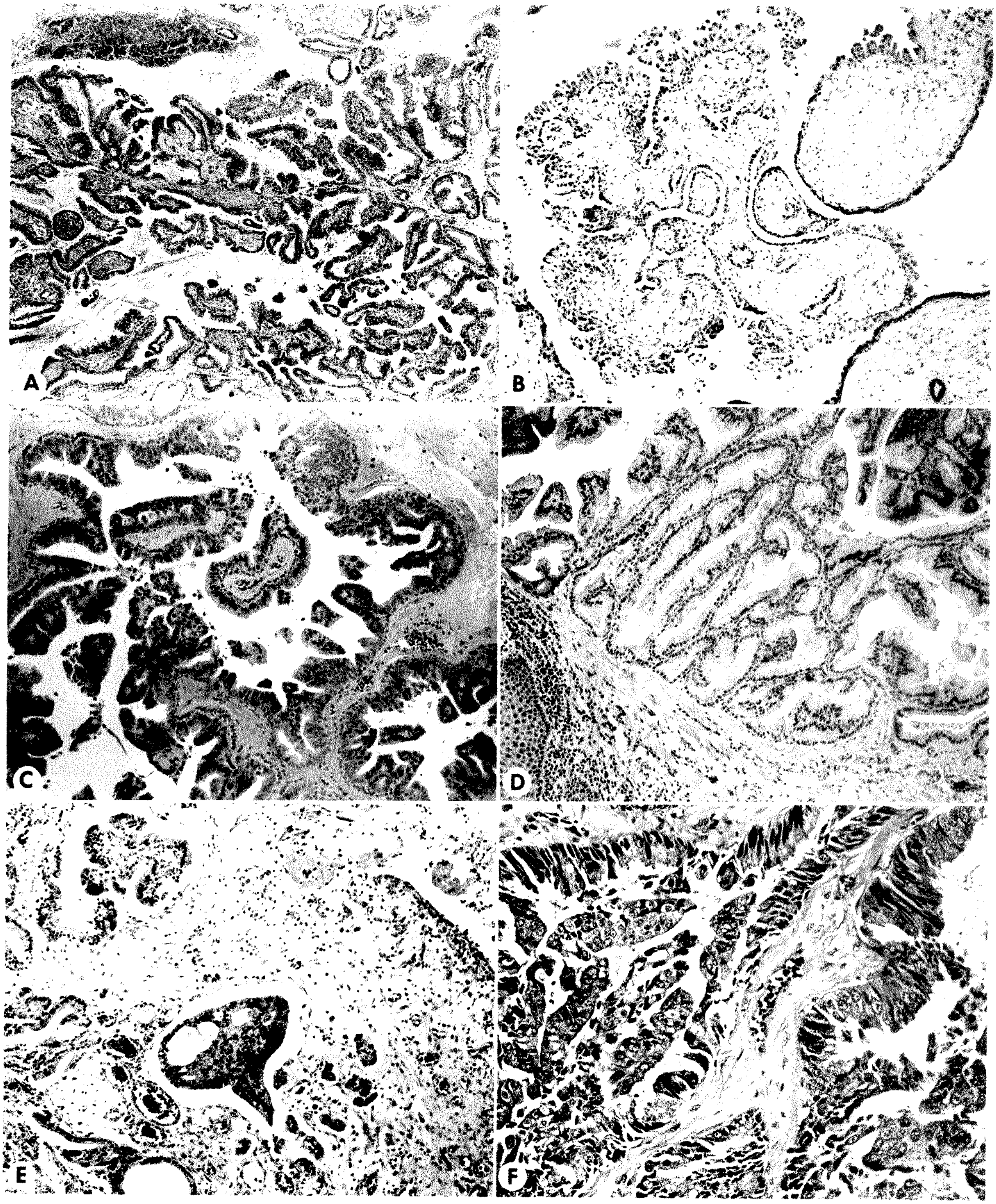

Fig 2. "Adenocarcinomas, not otherwise specified." A) Papillocystic adenocarcinoma of parotid gland (H & E, original x60). B) Another papillocystic adenocarcinoma of parotid gland (H & E, original x60). This variant has thick stromal papillae in contrast to one in A. C) Papillary adenocarcinoma of parotid gland (H & E, original x140). Major duct origin is evident in this well-differentiated carcinoma. D) Mucinous papillary carcinoma of buccal minor salivary gland (H & E, original x140). This adenocarcinoma is histologically low grade and was not infiltrative. E) Adenocarcinoma of sublingual gland (H & E, original x60). Although moderately differentiated, carcinoma has invaded lymphatic spaces. F) High-grade and invasive adenocarcinoma of parotid gland with histologic resemblance to gastrointestinal carcinoma (H & E, original x180).

the rubric of mucus-producing adenopapillary (nonepidermoid) carcinoma.

Given the degree of uncertainty and ambiguity of authors' classifications, it is not possible to give an incidence or site predilection for what remains of the adenocarcinoma NOS group of salivary carcinomas. In some reports, the statistical data are further distorted by including adenocarcinomas of mucosal surface origin, eg, many of the adenocarcinomas of the sinonasal tract.[10] Adenocarcinomas, not further defined, constituted 9% of all salivary neoplasms reported by Spiro et al.[7] Seifert and Schulz[8] record an incidence of 1.2%. The lesser number is closer to the truth.

As we have implied, the defining and extracting of clinicopathologic entities from the adenocarcinoma NOS classification is not just an academic exercise. The Table[4] on salivary duct (cribriform salivary carcinoma of excretory ducts) carcinoma emphasizes this in its relating the very poor prognosis associated with the carcinoma, an outlook that cannot be transferred to all adenocarcinomas.

What are some of the unifying features of the residue of the adenocarcinomas NOS? They are the least common of the generic adenocarcinomas and are preponderantly neoplasms of the major salivary glands, especially the parotid glands. All appear to arise from the excretory or intermediate (nonintercalated) parts of the salivary duct unit. Most manifest a histopathologic appearance that would be designated adenocarcinoma at any anatomic site, and they may resemble adenocarcinomas of the lungs, breast, or gastrointestinal tract. The neoplasms may be solid or cystic, may be circumscribed/encapsulated or infiltrative, may be papillary or nonpapillary, and may produce mucin or be devoid of this secretory product (Fig 2). Patient age at diagnosis can cover the entire life span, but the neoplasm's highest frequency is in the sixth and seventh decades.[6] There appears to be a modest predilection for females. A high histopathologic grade, an abnormal nuclear DNA content, an infiltrative growth pattern, and large size adversely affect outcome.[11] Perhaps because these features are less often seen in the oral adenocarcinomas, such neoplasms have a better outlook than the major salivary gland adenocarcinomas.

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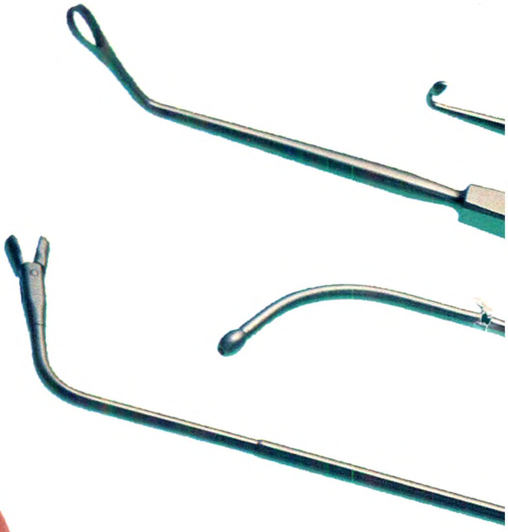
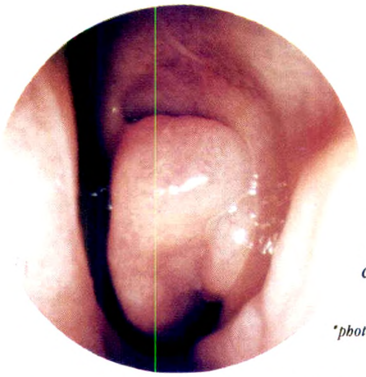
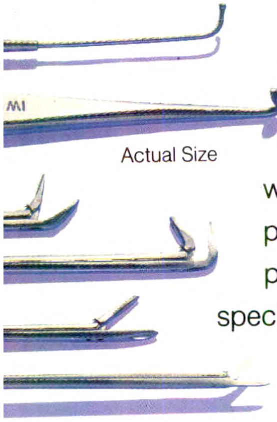




*Concha bullosa on left side bulging into lateral nasal wall. Entrance to middle meatus blocked and a polyp is arising from the contact area.**

**photo by Professor H. Stammberger*



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VOL. 59 MARCH, 1950 No. 1

THE TRANSMISSION PROPERTIES OF THE MIDDLE EAR

ERNEST GLEN WEVER, PH.D.
AND
MERLE LAWRENCE, PH.D.
PRINCETON, N. J.

The basic function of the middle ear mechanism is well known: it serves as a mechanical transformer, providing for the ready transfer of acoustic energy from the outside air to the fluid of the cochlea. Without such transformer action the vibratory motions of the air particles would not easily be communicated to the heavier particles of the cochlear fluid, but to a large extent would be reflected back from the boundary. When given the proper mechanical advantage, which produces an increase in the pressure, the transfer of energy is made without loss.

We have studied this action of the middle ear in experimental animals in which exact measurements of the ear's operation may be made in terms of the cochlear potentials.[1] Most of the work has been carried out in the cat, a particularly favorable animal for this

---

From the Princeton Psychological Laboratory. This research was supported in part by the Office of Naval Research, under Contract N6-onr 270, T. O. 3, Project NR 145-322. Permission is granted for reproduction, translation, publication, use and disposal in whole or in part by or for the United States Government.

investigation. We have found that a complete removal of the middle ear, except for the footplate of the stapes, results in a serious loss of sensitivity for all tones. The loss is greatest for the middle frequencies, for which it is about 33 db, and somewhat less for the low and high frequencies, for which it is about 25 db; the over-all average of the loss is 28 db. When we calculate the contribution to the sensitivity that an ideal transformer action should give we obtain a value of 30 db. The observed average of 28 db thus signifies that the middle ear mechanism is remarkably well adapted to its purpose.

In our consideration of this problem we have paid attention to the principle upon which the transformer action is based. From the evidence now at hand there seems little doubt that the mechanical advantage is secured mainly, and perhaps solely, through the difference in areas of tympanic membrane and stapes footplate. The pressure of the transmitted waves is enhanced in proportion to the areal ratio of these surfaces.

What has just been said refers to the principle of the transformer action, yet we are still far from an understanding of the specific manner in which this action is achieved. We need to know more about the acoustical properties of the middle ear.

A mechanical transformer, though simple enough in conception, is a particularly difficult mechanism to construct. Such a transformer ought merely to provide a means for one medium to act upon another, without interposing properties of its own upon the action pattern. No real transformer fills this requirement perfectly; every mechanism has peculiar response characteristics that disturb the action. The difficulties with such a mechanism grow increasingly serious when it is required to operate over a wide frequency range.

No man-made mechanical transformer with which we are acquainted even approximates the quality of the middle ear. A comparable instrument is the early type of phonographic recorder, in which the motions of a diaphragm are communicated to a stylus that inscribes a wave on a wax surface. The poor performance of this instrument is well known. It has become obsolete for this reason, having given way to much more elaborate arrangements of electromechanical devices that permit the inclusion of electronic circuits for increasing the sensitivity and correcting for the bad frequency characteristics. Even these modern arrangements do not often have any outstanding qualities of range and fidelity.

As we perceive these engineering difficulties we gain an added appreciation of the instrument that Nature has developed, and of its fabrication out of such seemingly crude materials as fiber and bone. Our task is to examine further the properties of this instrument.

One of the ways in which the acoustical properties of a system are revealed is through the changes of phase that the system introduces into the vibratory motions that it transmits. The present study represents an attempt to treat the middle ear by this method. As will soon be clear, this method is most profitable when carried out simultaneously with determinations of the sensitivity of the mechanical system.

EXPERIMENTAL PROCEDURES

These experiments, like the others already referred to, were performed on the cat, and by using the electrical potentials of the cochlea. The animals were deeply anesthetized with a solution of diallylbarbituric acid injected intraperitoneally, and in nearly all instances they were further immobilized with curare. The curare was injected into the femoral vein in an amount sufficient to suppress all reflex activity, and the animal then was maintained for the duration of the experiment by artificial respiration. The observations were made on 20 ears.

The auditory bulla was approached by the mediolateral route and opened sufficiently to give access to the round window. A platinum foil electrode was placed in contact with the round window membrane and an indifferent electrode was inserted in muscle tissue near by.

The further operative procedures were carried out in two stages. In the first stage the pinna and the membranous part of the external auditory meatus were removed, thereby exposing the drum membrane to clear view. An acoustic probe was inserted into the remaining meatal cavity as near to the drum membrane as was considered safe—within about 2 mm. A sound tube leading from a loudspeaker was placed near the meatal orifice and then this region was sealed over with wax. The sound tube and probe tube thus were enclosed in a small cavity whose inner boundary was the drum membrane.

The acoustic probe consisted of a narrow tube, 1.6 mm in outside diameter, 0.88 mm in inside diameter, and 63.5 mm long. It led to a cap fitted close to the diaphragm of a condenser microphone (Western Electric miniature microphone Type 640-AA). This probe-microphone combination permits the recording of sounds in narrow places, places impossible of access with the microphone itself. The combination, with its associated amplifier, is calibrated to show the sound pressures present at the probe tip.

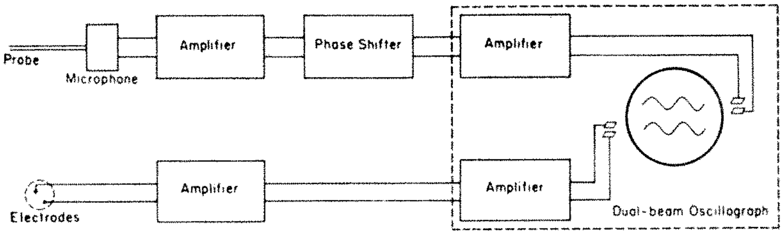

Fig. 1.—Apparatus arrangement for phase measurements.

The acoustic probe and microphone were used also to indicate phase relations. The arrangement for this purpose is shown in Fig. 1. The currents from the microphone amplifier were run through a phase shifter to one side of a dual cathode-ray oscillograph. At the same time, the cochlear potentials picked up from the round window membrane were run through an amplifier to the other side of the dual oscillograph. This oscillograph employs a dual-beam tube: two separate electron streams impinge upon the same tube face and give separate waves that may be placed side by side for comparison.

The microphone and cochlear potential signals were connected to the oscillograph so as to give vertical deflections on its tube face, while the sweep circuit of the instrument gave synchronized horizontal deflections. The same sweep was used for both beams, so that when the two signals were in phase the resulting waves could be made to coincide if suitably adjusted in amplitude and in vertical position on the tube face. When the signals were out of phase the waves were displaced in the lateral dimension with respect to one another. They could be brought into coincidence then only by manipulating the phase shifter in the microphone circuit.

Our procedure at this stage consisted of presenting a tone to the animal's ear and adjusting the phase shifter for coincidence of the stimulating and response waves. The reading of the phase shifter was then recorded. This reading includes the phase characteristics of all the apparatus and of the ear; it has no absolute significance. Such readings were obtained for numerous tones—often as many as 60 to 70—over the range from 100 to 10,000 cycles.

Then the second stage of the operation was carried out. The drum membrane was removed and the incudostapedial joint was broken, after which the malleus and incus were removed. The stapes was left in position in the oval window, with its tendon still attached. Special care was taken to avoid injury to the oval window.

The probe tube was inserted deep in the middle ear cavity, close to the stapes. The sound tube remained in its former position at the meatal orifice, and again the region was sealed over with wax.

Now, with the same tones as used before, the phase shifter again was adjusted for coincidence of the waves representing the sound stimulus and the cochlear response, and its readings noted. A comparison of this series of readings with the series taken earlier reveals the effect of the removal of the middle ear structures upon the phase of the transmitted sound.

Along with these observations of phase we carried out measurements of sensitivity in the usual manner. Using the same tones, both before and after the middle ear operation, we ascertained the sound pressure necessary to produce a standard amount of cochlear response. The differences between these sets of measurements represent the middle ear's contributions to sensitivity.

The observations of phase incur certain technical difficulties. To obtain the necessary stability of the measuring apparatus it is necessary to give special attention to its design and adjustment and to make frequent checks of calibration. Particular difficulties were experienced at 100 cycles. At this frequency our loudspeaker gave only a small output before it suffered overloading as shown by nonlinearity and distortion of wave form. Unfortunately also the sensitivity of the cat's ear at this frequency is rather poor. Consequently the signals obtained were small and background noise was disturbing, so that the measurements are not very reliable. At higher frequencies, however, it usually was possible to repeat the measurements within 5.° This remained true after ordinary readjustments of the stimulating arrangement: the wax seal could be removed, the probe tube shifted to a new position, and the seal restored, without altering the readings.

RESULTS

Figure 2 shows the phase observations on 4 ears. Each curve represents for a given ear the changes of phase undergone by the transmitted wave due to the presence of the middle ear apparatus. The changes are shown on the ordinate as positive (signifying a retardation of phase) or as negative (signifying an advancement of phase) for various frequencies as given along the abscissa.

The pattern of phase changes is remarkably similar for the different ears, though there are variations of detail. The similarity is especially striking over the lower half of the frequency range, from 150 cycles up to 2000 cycles. Over most of this range, up to 1000 cycles, the middle ear produces a small and fairly uniform advance-

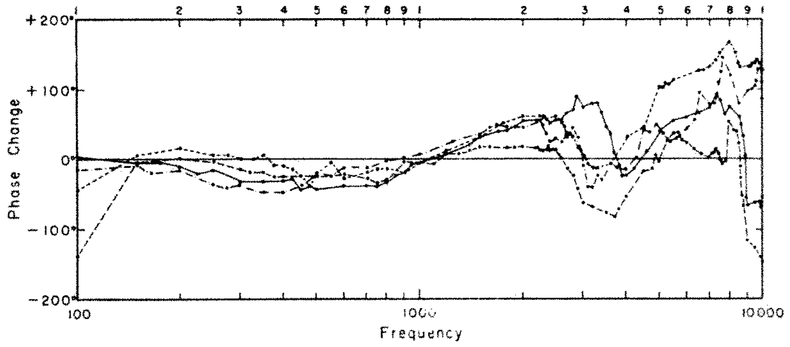

Fig. 2.—Phase changes introduced by the middle ear into the sounds that it transmits. Positive degrees represent phase retardation; negative degrees represent phase advancement.

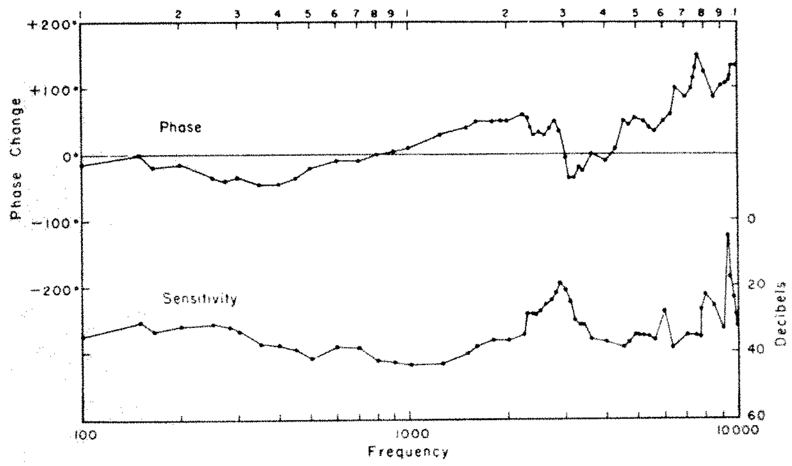

Fig. 3.—Phase changes in the middle ear in relation to its contributions to sensitivity. For the upper curve use the left-hand ordinate scale, and for the lower curve use the right-hand ordinate scale.

ment of phase, never exceeding 40.° Just above 1000 cycles the curves cross the zero line, and here the transmission occurs without phase change. For higher tones the phase change is contrary in direction: the conducted wave lags in phase behind the entering wave. The lag grows in amount to a maximum whose frequency location varies in the different ears from 2000 to 3000 cycles, whereupon the curves fall sharply and cross the zero line again. The points of these crossings vary from 2600 to 3750 cycles. The curves attain a rather sharp minimum, representing the utmost of advancing phase in this region, and then once more rise and cross the zero line. They make this crossing in the region from 3800 to 5000 cycles. In the remaining high-frequency region are the largest variations. Two of the curves remain above the zero line, representing phase lag, and undergo a few undulations there. The other two, likewise undergoing rapid changes, end below the zero line.

These phase changes that the middle ear introduces become more meaningful when viewed along with the changes of sensitivity. The relations are shown for one ear in Fig. 3. Here the upper curve represents phase changes as before and the lower curve represents in decibels the gain in sensitivity afforded by the middle ear.

As we have found earlier, the sensitivity function for the middle ear contains two regions of relatively high sensitivity separated by a sharp peak of low sensitivity. As represented in Fig. 3, the minimum portions of the curves are regions of maximum sensitivity. The first of these regions is very broad; the curve declines slowly with frequency to the region of 1000 cycles and then rises a little more rapidly. Note that this minimum corresponds approximately with the frequency where the phase curve changes from negative to positive. The sharp peak in the sensitivity curve has its maximum (point of poorest sensitivity) near 3000 cycles. This is the frequency where the phase makes a change in the contrary direction, from positive to negative. The second minimum of the curve (maximum of sensitivity) lies between 4000 and 5000 cycles. In this region the curve of phase change again crosses from negative to positive. For still higher frequencies both the sensitivity and phase functions show further variations, but in general the sensitivity is falling while the phase is growing more and more retarded.

DISCUSSION

On the basis of the results before us we now proceed in our effort to ascertain the mechanical properties of the middle ear. A mechanical system that only transmits vibrations and does not itself produce them consists of just three types of elements: masses, compliances, and mechanical resistances. The mass of a body represents (among other things) its ability to store energy on being set in motion. Compliance is a property that characterizes a spring: a spring gives way to an applied force, and at the same time exerts a force in opposition. Thus a spring also is able to store energy. Alternatively we speak of a spring as having stiffness, which is the inverse of the compliance. Mechanical resistance is the friction produced by the motion of a body as its parts slide on one another or on fixed structures near by and in so doing use up a part of the applied energy by converting it into heat.

Any analysis of the conductive properties of the middle ear must ultimately be made in the terms just given, but such an analysis is difficult to carry out directly. Rather, we resort to a method of analogies, as is common practice in dealing with complex vibratory systems. In this method we first consider the forms of electric circuits that possess the same phase and sensitivity characteristics as shown by the middle ear, and then by means of analogical relations we translate the electrical properties into mechanical ones. This procedure has the advantage of an extensive fund of experience with electric networks, gained through the work carried out in recent years on various forms of communication systems. On the basis of this experience our insights are richer and better guided than if we dealt with the problems immediately in mechanical terms.

It is important in this connection to point out that the analogies with which we shall deal are not merely connotative, but hold in the strictest sense. This is so because the mathematical expressions relating the variables in one system are identical in form with those in the other system. Hence if we know the form of action for one system we can fully predict it for the analogous system. It may be added further that our actual data consist of electrical measurements, and that to regard them as representing the motions of the air and of the ear we have to rely on certain constant electromechanical relations. In other words, all our acoustic determinations involve functional dependencies between electrical and mechanical systems, and the analogies are only logical developments of these relationships.

Like the mechanical system discussed above, an electrical system that is merely transmissive contains only three types of elements. They are inductances, capacitances, and electrical resistances. Inductance is the property of a coil of wire; it opposes the passage of an electric current both as the current is introduced and as it is withdrawn. Temporarily it stores energy in a magnetic field, an action analogous to the storage of mechanical energy by a mass.

Capacitance is the property of a condenser, which consists of a pair of conducting plates separated by an insulator. When an electric charge is placed on one of the plates a charge of opposite polarity is induced on the other plate and a stress is introduced into the insulator. The condenser thus stores electrical energy much as a spring stores mechanical energy. Electrical resistance is the property of a conductor by virtue of which a passing electric current increases the molecular motions of the substance of the conductor, so that part of the impressed electrical energy is converted into heat.

The kind of opposition to the flow of alternating current that an inductance causes is known as positive reactance; its amount increases progressively with the frequency. The kind of opposition that a condenser causes is known as negative reactance, and its amount varies inversely as the frequency. It is also characteristic of an inductance to retard or lag the phase of the alternating current passing through it, whereas a capacitance advances the phase of the conducted current.

In our analogical system, mass corresponds to inductance, compliance to capacitance, and mechanical resistance to electrical resistance.

Now let us regard the results of Fig. 2 and 3 as representing the behavior of an electric network, and consider what arrangement of inductances, capacitances, and resistances would produce such effects in response to different vibratory frequencies. To simplify the problem somewhat at this point we consider the curves only over the principal portion of the range, neglecting the variations around 100 cycles and above 8000 cycles where experimental conditions and individual differences present particular difficulties.

In the low-frequency region, up to about 1000 cycles, the function shows a negative phase change. Imposed currents with frequencies within this range are advanced in phase. The representative electric network therefore must be one in which capacitative reactance is predominant within this frequency range. Above 1000 cycles and nearly to 3000 cycles, however, the phase change is positive or lagging, which means that for this range the inductive reactance of the network must be predominant. Then above 3000 cycles, as the phase change again becomes negative, the capacitative reactance again is predominant, and, finally, for the upper frequencies the phase change is positive and inductive reactance once more is predominant. At those frequencies at which the function crosses the zero phase line the inductive and capacitative effects are balanced

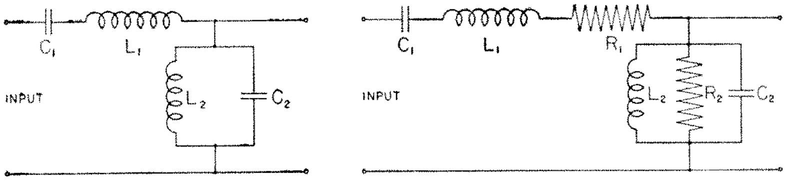

Fig. 4.—Electric networks presented as "models" of the middle ear mechanism. Circuit *a*, on the left, contains only inductances (L_1, L_2), and capacitances (C_1, C_2), whereas circuit *b*, on the right, includes resistances (R_1, R_2) also.

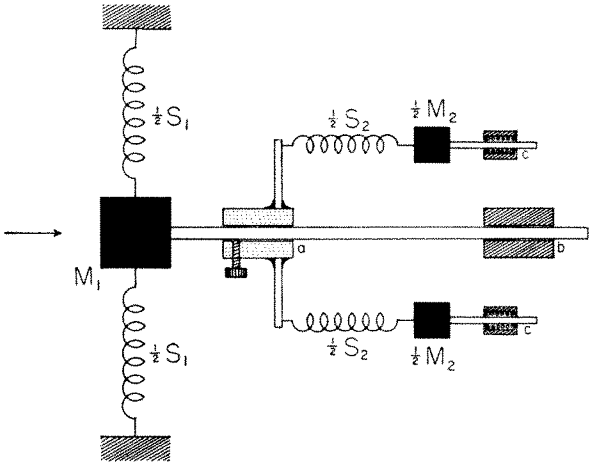

Fig. 5.—The mechanical counterpart of Fig. 4. With the proper conceptual changes this diagram will serve as the analogy for either circuit *a* or circuit *b* of that figure. M_1 and M_2 are masses, S_1 and S_2 are springs, *a* is a link, *b* and *c* are bearings. The cross-hatched parts are immobile.

For one condition, when serving as the analogy of circuit 4*a*, link *a* is rigidly attached to the central shaft by means of the thumb screw and bearing *b* is frictionless. For the other condition, when serving as the analogy of circuit 4*b*, bearing *b* is assumed to contain friction F_1, and the thumb screw of link *a* has been loosened and friction F_2 in this link governs the transfer of motion to S_2 and M_2. Under both conditions, bearings *c* are frictionless, and all shafts and link *a* are massless.

and their net reactance is zero. When the crossing is upward, and negative reactance gives way to positive reactance, we have a point of resonance, and when the crossing is in the contrary direction, and positive reactance gives way to negative reactance, we have a point of antiresonance. There are two resonance points, one around 1000 cycles and another varying in location in the different curves between 3800 and 5000 cycles, and interposed between them is an antiresonance, varying in location from 2600 to 3750 cycles.

As an approach to the disclosure of a responsive system with the properties just described let us first consider a relatively simple electric circuit, one containing four circuit elements, two inductances and two capacitances. There are four ways in which these elements may be arranged, and the arrangements are electrically equivalent if the elements are given the proper values. One arrangement is shown in Fig. 4*a*. It consists of a capacitance C_1 and an inductance L_1 in series, followed by a capacitance C_2 and an inductance L_2 in parallel. The reactance of this circuit varies with the frequency in the following manner. At zero frequency the reactance is negative, and infinitely large. As the frequency rises this negative reactance grows less, at first rapidly and then more slowly, until it reaches zero at a frequency f_1, the first resonance frequency. Above f_1 the reactance is positive, and rises precipitously to infinity as the frequency approaches f_2, an antiresonance frequency. At f_2 the function becomes discontinuous, suddenly vanishing at positive infinity and reappearing at negative infinity. Above f_2 the negative reactance progressively grows smaller until it is zero at f_3, the second resonance frequency. Above f_3 it is positive, and rather gradually approaches positive infinity as the frequency becomes infinitely high.

This function has the desired form except for the wide range of variations and the discontinuity at the point of antiresonance. However, these undesirable features vanish under practical conditions. In hearing we are not concerned with frequencies near zero and infinity. Also, real circuits always contain resistances along with the other elements, and in the presence of resistance there are no discontinuities in the function. Instead of jumping from infinitely positive to infinitely negative reactance at the antiresonance frequency, the function simply falls more or less rapidly from positive to negative through zero.

The introduction of resistances into the suggested circuit is shown in Fig. 4*b*. These resistances have further desirable effects. They greatly reduce the amount of the phase change introduced into the transmitted signal. At the same time they reduce the magnitude of the peaks of response at resonance frequencies and of the diminution of response at antiresonance frequencies. From Fig. 2 and 3 it is evident that a high value of resistance is effective about the first resonance point f_1 and a somewhat smaller value about the antiresonance and second resonance points f_2 and f_3. This we infer because in the lower frequencies the variations of phase are small and the resonance curve is very broad, whereas in the higher frequencies the phase variations are larger and the response more rapidly changing. The antiresonance, shown best in Fig. 3, is particularly abrupt.

We are now ready to turn back to the ear and to translate our electrical conceptions into the mechanical form. If we consider first the analogy to the simpler circuit of Fig. 4*a* we shall have a mechanical system consisting of two masses and two springs (compliances). The first mass M_1 is acted upon directly by the applied force, and is attached to the spring S_1 in such a way that when it is moved away from its equilibrium position the spring tends to bring it back. The second mass M_2 is not acted upon directly by the force, but is attached to the first mass through a spring S_2. This mechanism is pictured in Fig. 5, where the black squares are masses, the coils are springs, and certain shafts and bearings are provided to link the elements together. (In the drawing the springs S_1 and S_2 and the mass M_2 have been split into symmetrical halves in order to present an appearance of dynamical balance; this arrangement makes no difference otherwise.) At this point we are to suppose that the linkage at *a* is a rigid one, having been made so by means of the thumb screw, and the bearings *b, c* are frictionless. Also, the link *a* and all the shafts are to be considered massless.

This same diagram will serve to represent the mechanical counterpart of Fig. 4*b*, if now we think of bearing *b* as containing friction and the thumb screw of link *a* as having been loosened so that the coupling between central and side shafts depends upon friction. The friction F_1 in bearing *b* uses up some of the energy communicated to the mass M_1, and the friction F_2 in link *a* uses up some of the energy that would otherwise be transferred to S_2 and M_2.

Our final consideration is the possibility of identifying the elements M_1, M_2, S_1, S_2, F_1, and F_2 in terms of anatomical structures in the ear. We present the following as a reasonable hypothesis.

The mass M_1 is the mass of the malleus, incus, and drum membrane, and other parts that move strictly in phase with them. The spring S_1 is partly in the drum membrane and partly in the suspension system of the middle ear. The spring S_2 is wholly in the suspension system: in the attachments afforded by the anterior and lateral ligaments of the malleus and its wing process, the posterior ligament of the incus, and the tensor tympani tendon. The mass M_2 is partly in this suspension system and partly in the structures to which the suspending elements are moored. These mooring structures add to the mass because they are not altogether rigid, but are somewhat involved in the motions. The friction F_1 is the friction generated by the movements of mass M_1. It includes the sliding of fibers of the drum membrane over one another, which occurs especially near its outer edge where the central motion grades down to zero under the restraint afforded by the tympanic ring. It includes also a part of the friction produced in the ligaments and the tensor tympani tendon, and especially that produced in their more proximal portions. The friction F_2 is generated in the movements of mass M_2, and it arises in the more distal portions of the suspensory elements as their fibers move on one another or over fixed structures.

CONCLUSIONS

Our observations have been limited to the cat, and necessarily our conclusions have direct application only to this species. At the same time, however, the possibility is presented to us that other ears, including man's, have made adaptations of function that are as serviceable as the ones revealed in this animal.

We find that the middle ear apparatus—or, rather, that part of it peripheral to the stapes—fulfills its duties as a mechanical transformer with only slight disturbances of the response pattern. It presents to the stimulating sounds an impedance that varies remarkably little with frequency. It does this because it is a doubletuned and highly damped system. To the single stiffness and single mass that would have to be present in order for the structure to act as a mechanical transformer have been added a further stiffness and mass, with the result that we have a system resonant to two separated frequencies. At the same time, the action is subjected to considerable frictional damping, so that the resonances are very broad.

We have so far left out of account the behavior of the system at the extreme frequencies, for the reasons given. The results at the lowest frequencies suggest that the response continues to be more uniform at this end of the scale than we ought to expect from a system containing only four reactive elements (two masses and two compliances). If further investigation supports this suggestion it will be necessary to add one more reactive element to our representative scheme.

We believe that the variations found at the upper frequencies represent inherent instabilities in the mechanism: variations in the tensions of the suspensory structures, and perhaps also in the effective mass which they present. Especially must we expect a variation in the tension exerted by the tensor tympani tendon, even though under our conditions the action of its muscle was largely prevented by curarization.

The part of the middle ear apparatus that has been excluded from this discussion, the stapes and its tendon, will be considered later by a somewhat different method. It will suffice to say now that over the major portion of the auditory range this part has only a very slight effect upon the action of the system. That action, as we have seen, commands our respect as an achievement in mechanical engineering and in the service of hearing.

SUMMARY

The characteristics of the middle ear apparatus have been investigated in terms of the changes of phase and magnitude that this apparatus introduces into the sounds that it transmits. The work has been carried out on the cat by means of the cochlear potentials. The results show that the middle ear in this animal presents remarkably uniform properties to sounds over a wide range of frequencies. An analysis based upon electrical and mechanical "models" indicates that this uniformity is achieved by the development of two mechanical resonances separated by about two octaves and by the presence of a high degree of frictional damping. In consequence, the middle ear is able to carry out its function as a mechanical transformer with minimum disturbance of the response pattern.

We are indebted to the Bell Telephone Laboratories and the Western Electric Company for the loan of calibrated microphones used in this research.

PRINCETON UNIVERSITY.

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TREATMENT OF TRACHEAL AND ENDOBRONCHIAL LESIONS WITH THE POTASSIUM TITANYL PHOSPHATE LASER

ROBERT F. WARD, MD
NEW YORK, NEW YORK

Lower tracheal and endobronchial lesions represent a difficult management problem. While there has been some success in the treatment of these lesions with the carbon dioxide laser, the limitations of its delivery system have restricted its use in infants and neonates. The potassium titanyl phosphate (KTP) laser, transmitted via a flexible quartz fiber, can be precisely manipulated even through rigid pediatric bronchoscopes as small as 3.0 mm. In addition, the Hopkins telescopic lens may be used to improve visualization and control. We report our experience using the KTP laser to treat 15 pediatric patients with tracheal and endobronchial lesions. The nature of the lesions, the details of the technique, and the results are presented.

KEY WORDS — endobronchial lesions, endoscopy, potassium titanyl phosphate laser, tracheal lesions.

INTRODUCTION

The management of acquired lesions of the tracheobronchial complex continues to be a difficult clinical problem, especially in the neonatal and pediatric age groups. Endoscopic methods of correction have been developed, including traditional bronchoscopic dilation as well as laser excision or ablation. The advent of microscopic laryngoscopy, bronchoscopic telescopes, and the carbon dioxide (CO2) laser has significantly advanced the treatment of these challenging problems.[1-4] The microsubglottiscopes can be coupled with the operating microscope to allow for binocular visualization with magnification.

Likewise, the CO2 laser bronchoscope has been used in the treatment of these lesions by means of a ventilating bronchoscope with an attachable endoscopic coupler.[5,6] Recent reports have discussed its application in patients as young as 6 months.[7] The major limitation to this technique, however, is the inability to use bronchoscopes smaller than 4.0 mm (outside diameter 7.0 mm).[8] Additionally, at this small size, visualization is compromised.

The development of various laser wavelengths that can be delivered through flexible fibers has provided even newer modalities to treat tracheal and endobronchial lesions. Laser fibers may be passed through telescopic bronchoscopes, both rigid and flexible, to reach lower tracheal lesions. Our experience using the potassium titanyl phosphate (KTP) laser in the treatment of tracheal and endobronchial lesions has been promising. The KTP laser belongs to the family of solid-state lasers. The yttrium aluminum garnet (YAG) crystal with a wavelength of 1,064 nm is modified by a crystal of potassium titanyl phosphate to produce a 532-nm wavelength. This produces a visible green light.

METHODS AND MATERIALS

The KTP laser was employed in the treatment of tracheal and endobronchial lesions in 18 patients between the years 1988 and 1990. Of these, 15 were in the pediatric age group, ranging from newborn to 13 years old. The type of lesion treated, as well as patient information, is shown in the Table. A total of 21 procedures were performed on the 18 patients. Excluded were patients with respiratory papillomatosis.

All procedures were performed in the operating room under general anesthesia. Standard laser precautions, including cutaneous and ocular protection of the patient and ocular protection of the staff, were observed. Anesthesia was delivered by way of an existing tracheotomy tube, venturi ventilation attachments to the subglottiscopes for upper tracheal lesions, and most commonly the ventilating port of the pediatric bronchoscope.

The trachea was examined with the appropriate-size Storz, Doesel-Huzly pediatric rigid bronchoscopes, as small as 3.0 mm (outside diameter 5.0 mm), with a 0° Hopkins rod magnifying optical telescope. The procedures were then performed with either the quartz fiber of the KTP/532 laser (Laserscope) or by using the KTP/532 micromanipulator. When the quartz fiber is used, the fiber is passed down the suction port of the Storz bronchoscope. The fiber can be used in a contact or noncontact manner.

From the Department of Otolaryngology, The New York Hospital–Cornell Medical Center, New York, New York.

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REPRINTS — Robert F. Ward, MD, Dept of Otolaryngology, The New York Hospital–Cornell Medical Center, 525 E 68th St, New York, NY 10021.

SUMMARY OF CASES

Pt	Age	Tracheotomy Tube	Diagnosis
1	5 y	Yes	Tracheal stenosis and malacia
2	Neonate	No	Status post tracheal and carinal resection for congenital stenosis
3	9 mo	No	Subglottic cysts
4	1 y	No	Tuberculosis granuloma, left bronchus
5	5 y	Yes	Suprastomal granuloma
6	9 mo	No	Tuberculosis granuloma, right bronchus
7	18 y	Yes	Tracheal stenosis
8	25 y	No	Midtracheal stenosis from intubation injury
9	6 y	Yes	Tracheal stenosis with anteroposterior adhesions
10	15 y	Yes	Suprastomal stenosis; status post near-drowning accident
11	1 y	No	Tracheal cysts
12	4 y	Yes	Congenital laryngotracheal stenosis
13	13 y	No	Status post laryngotracheoplasty at age 3; subglottic granuloma
14	44 y	No	Tracheal stenosis from intubation; underwent tracheal resection
15	13 y	No	Laryngeal and subglottic stenosis
16	13 y	Yes	Lymphoma with extrinsic tracheal compression; developed tracheal stenosis
17	3 y	Yes	Subglottic web (lateral)
18	7 y	Yes	Status post laryngotracheoplasty; developed subglottic cysts, granulation tissue

The laser was set to deliver 3 to 5 W of power, with an average of 5 W, with either a continuous or pulsed function. The system has also been used with a flexible bronchoscope by using the suction port for fiber placement.

All patients remained in the hospital overnight after their procedures. Patients were given intravenous Decadron when there was a concern over laryngeal or subglottic edema and when medically safe. Postoperative humidification and racemic epinephrine were employed as necessary.

RESULTS

In the 15 pediatric patients treated with the KTP laser, there were four types of disorders encountered: 1) granulomas or granulation tissue associated with some type of mechanical trauma (eg, endotracheal tube or tracheotomy; these included suprastomal granulomas), 2) granulomas of tuberculous origin, usually causing obstruction of either main bronchus and subsequent postobstructive pneumonia, 3) subglottic and tracheal cysts associated with mucosal injury from intubation, and 4) a variety of mature tracheal stenoses, including webs, shelflike tracheal narrowing, and circumferential cicatricial stenosis.

The children with granulomas or granulation tissue in general showed a better response to treatment, with the resolution of their obstruction. Similarly, the cystic lesions responded well to this treatment. Cicatricial scars did not respond well to laser therapy alone, as has been supported in previous reports.[9,10]

There were no serious complications directly related to the actual endoscopic laser procedures performed. One child (patient 2) developed an eschar at the level of the carina, where granulation tissue had been lasered. He developed respiratory distress on postoperative day 1 that required return to the operating room for endoscopic removal of the lower tracheobronchial debris. This child eventually succumbed to progressive cicatricial narrowing of his lower trachea and bronchi, approximately 1 year after the initial resection of a congenital tracheal stenosis with complete cartilaginous rings involving the lower trachea and carina.

Patient 11 developed significant bronchospasm at the end of the laser procedure that responded to bronchodilators. He was able to be extubated after the procedure without further respiratory compromise.

No postoperative bleeding was encountered during or after any laser procedures.

DISCUSSION

Endoscopic management of tracheobronchial lesions, both benign and malignant, has been well established over the last decade.[2,5,10-14] The laser has become part of the armamentarium to further enhance this modality by allowing "hands-off" surgery through the ventilating bronchoscope. It has also provided increased hemostasis and precise control of the ablation.[10]

The mainstay of laser endoscopy has been the CO2 laser for certain pathologic conditions because of its greater or more precise cutting properties.[15,16] However, the CO2 bronchoscopic delivery system has proven to have limited use in the neonate and young infant, especially when dealing with lower tracheal or endobronchial lesions. The endoscopic coupler can only be used with the 4.0-mm (outside diameter 7.0 mm) or larger bronchoscope. With this size bronchoscope, visualization is diminished and there may be significant scatter from the helium neon aiming beam, making visualization further limited. This limitation has been able to be overcome to some measure by using the CO2 laser with several types of subglottiscopes that have allowed access to the lower trachea and carina.[1,17,18] When the subglottiscope is coupled to the operating microscope, greater precision can be achieved with the advantages of binocular vision and magnification.

The laser energy of the KTP laser can be transmitted through a flexible quartz fiber and delivered to tissues by both hand-held instruments and microscope attachments. This allows delivery of the KTP fiber of either 0.6 mm or 0.4 mm through the suction port of a rigid bronchoscope as small as 3.0 mm. This is used with the 0° Hopkins optical telescope, which provides excellent illumination and magnification. The fiber is directed by rotating the bronchoscope. In addition, the fiber can be used with a flexible pediatric bronchoscope in patients who can accommodate a 4.5-mm endotracheal tube.

Additionally, the fiber can be used in either a contact or noncontact manner without interruption of lasering. Since the KTP wavelength is 532 nm, there is no need for an aiming beam.

The disadvantages of the KTP laser when used through the bronchoscope with the Hopkins telescope include compromise of visualization by small amounts of blood or debris if they come in contact with the tip of the telescope. The procedures are also carried out with monocular vision, and thus there is some loss of the depth of field.

The KTP laser can be used to vaporize, incise, and coagulate and is preferentially absorbed by hemoglobin.[19] In similar situations, the KTP laser will produce twice as much tissue necrosis as the CO2 laser, yet its extinction is far less than that of the YAG laser. The tissue effects of the KTP laser differ from those of the CO2 laser, making it more applicable for specific lesions, eg, granulation tissue or hemangiomas. It would seem that certain wavelengths will eventually be discovered to be more advantageous for the treatment of certain lesions. The precise tissue effects of the various lasers available at the present time will need further verification and identification.

In our series, the KTP laser has been useful in treating various disorders of the trachea and lower airway. Because of the greater depth of penetration with the KTP laser, we still favor the use of the CO2 laser for treating laryngeal papillomatosis. In those children who have advanced tracheal or tracheobronchial papillomatosis who cannot accommodate the smallest bronchoscope that will attach to the endoscopic coupler, we would use the KTP laser. The KTP laser has been helpful and relatively safe in treating granulomatous and cystic lesions of the trachea and tracheal stenosis.

Certainly, the predictive factors of success or failure in the endoscopic management of tracheal stenosis described by Simpson et al[9] and Ossoff et al[10] apply to the pediatric age group. Circumferential, cicatricial stenosis greater than 1 cm, collapse of the cartilaginous support of the airway, and carinal involvement make endoscopic laser treatment less favorable. While these caveats were initially described with the CO2 laser, they appear to hold true for the KTP laser as well. In two patients, we have found the KTP laser to be a successful adjuvant in the treatment of stenotic lesions that improved the airway stenosis to allow for an open surgical procedure.[15]

Another alternative for the treatment of lower tracheal lesions in small children is diathermy. This has recently been reported to be effective for limited lesions of the airway, including laryngotracheal granulation tissue, papillomas, and vascular lesions such as small subglottic hemangioma.[20] The Storz Bugbee electrode may be used through a pediatric bronchoscope suction port to cauterize the unwanted tissue. Although requiring specialized training and safety modifications, if available the laser provides distinctly greater precision and less injury to the surrounding tissues.

CONCLUSION

The KTP laser with standard pediatric endoscopic instrumentation was employed in 15 pediatric patients in the treatment of tracheal and endobronchial lesions. This delivery system has overcome certain limitations experienced with the CO2 laser and offers an alternative approach for dealing with a variety of airway problems in the pediatric population. In addition, the specific tissue effects of the KTP laser may make it more desirable in the treatment of some airway lesions. This modality is proposed as an adjuvant to the endoscopic treatment of tracheobronchial lesions in the pediatric population.

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CONSERVATIVE MEDICAL MANAGEMENT OF TRAUMATIC PHARYNGOESOPHAGEAL PERFORATIONS

SANFORD R. DOLGIN, MD
THOMAS W. WYKOFF, MD
NARENDRA R. KUMAR, MD
ANTHONY J. MANIGLIA, MD
CLEVELAND, OHIO

Traditionally, surgical treatment has been the acceptable management for perforation of the pharyngoesophageal tract secondary to blunt and penetrating trauma. From July 1983 to June 1990, we managed 10 patients with this type of lesion by a conservative medical management approach. Mirror or fiberoptic flexible laryngoscopy was performed in the majority of cases to ascertain the nature of the injury. An esophagogram is very helpful to locate and evaluate the extent of the injury. All patients were treated with broad-spectrum intravenous antibiotic therapy and no oral feeding. There were no complications or need for surgical treatment in any of the cases. The head and neck surgeon, in selected cases, should consider the possibility of using conservative management of pharyngoesophageal perforations. This approach has proven in our hands to be relatively safe and cost-effective, resulting in no disability or prolonged hospitalization of our patients. This study involves two institutions (two affiliated hospitals of Case Western Reserve University School of Medicine) with different surgeons selecting appropriate antibiotic therapy. It is a retrospective review. No controls were made by random selection of cases treated surgically. These cases, if not properly managed, may lead to fatal outcomes.

KEY WORDS — antibiotic therapy, conservative management, pharyngoesophageal perforation.

INTRODUCTION

The choice of management of pharyngoesophageal perforations has been controversial. Traditionally, surgical closure has been the preferred approach since the late 1940s.[1-5] However, in the past 30 years, there have been numerous series advocating conservative medical management.[1-12] This approach relies heavily on early diagnosis and a high index of suspicion, institution of broad-spectrum intravenous antibiotic therapy, and no oral feedings. The most common cause of these injuries is iatrogenic, ie, instrumentation.[2,4,11] Esophagoscopy for diagnostic and therapeutic management has an incidence of perforation of 0.1% to 1% with rigid instrumentation and 0.01% with a flexible esophagoscope.[5] Bleeding and technical difficulty associated with the procedure should alert the operator to an increased possibility of injury.[1,12] The most common site for these perforations is the cricopharyngeal region.[11,13] Trauma secondary to endotracheal intubation is not a common occurrence and is usually due to a very difficult intubation or to the inexperience of the individual placing the tube, an emergent setting, or the use of a stylet with the procedure.[5,11,13,14] There are also reports of injury to neonates in intensive care units attributed to the use of rigid suction catheters, nasogastric and endotracheal tube placement, and digital trauma by the physician during resuscitative efforts.[15-17] Spontaneous rupture, foreign bodies, and blunt trauma are other noted causes.[4,5,11]

Signs and symptoms that are indicative of pharyngoesophageal injury are subcutaneous emphysema, pain, dysphagia, and sepsis.[1,12] In higher injuries, dysphagia, cervical pain, and subcutaneous emphysema occur commonly. With lower esophageal injuries, retrosternal and midthoracic pain, abdominal rigidity, and splinting of respiration can occur.[10,12] Radiographic (x-ray) studies usually confirm the above findings and additionally reveal the presence of pneumomediastinum and pneumothorax, and an esophagogram reveals the location of the injury by leakage of the contrast medium in the majority of cases.[1,5,8]

The patient should be followed up closely in a monitored setting once treatment is initiated. If the status of the patient deteriorates secondary to cervical or mediastinal abscess, then surgical drainage should be performed without delay.[5,17]

MATERIALS AND METHODS

A retrospective review from July 1983 to June 1990 at three institutions revealed a total of 10 patients sustaining traumatic pharyngoesophageal perforation that was managed conservatively (see Table). Conservative management of these patients included nothing by mouth, intravenous fluids and antibiotics, and nasogastric decompression with subsequent feeding if a nasogastric tube could be safely passed. There were no mortalities among this group and no failures of conservative management requiring surgical intervention.

From the Department of Otolaryngology–Head and Neck Surgery, Case Western Reserve University School of Medicine, Cleveland, Ohio.

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REPRINTS — Anthony J. Maniglia, MD, Dept of Otolaryngology–Head and Neck Surgery, 2074 Abington Rd, Cleveland, OH 44106.

PHARYNGOESOPHAGEAL PERFORATIONS

Case	*Age*	*Sex*	*Cause*	*Location*	*Time to Treatment From Injury*	*Intravenous Antibiotics Used*	*Time Until Oral Feeding*
1	26 y	M	Assault	Oropharynx and hypopharynx	<12 h	Ampicillin, clindamycin, gentamicin	10 d
2	21 y	F	Iatrogenic	Not found	12-24 h	Trimethoprim-sulfamethoxazole, metronidazole	3 d
3	79 y	M	Iatrogenic	Not found	<12 h	Cefazolin	10 d
4	45 y	M	Iatrogenic	Hypopharynx	<12 h	Netilmicin, clindamycin	5 d
5	57 y	M	Trauma	Oropharynx and hypopharynx	12-24 h	Cefazolin, metronidazole	10 d
6	39 y	M	Trauma	Hypopharynx	12-24 h	Cefazolin, metronidazole	8 d
7	45 y	M	Iatrogenic	Hypopharynx	<12 h	Cefazolin	5 d
8	92 y	M	Iatrogenic	Esophagus	<12 h	Cefazolin, metronidazole, gentamicin	Received gastrostomy
9	73 y	F	Iatrogenic	Hypopharynx	<12 h	Cephalothin, pencillin G	1 d
10	18 d	F	Assault	Oropharynx and hypopharynx	>24 h	Penicillin, gentamicin	8 d

The ages at the time of diagnosis ranged from 18 days to 92 years, with a mean age of 48 years. There were seven males and three females; six were white and four black.

The time period from injury to diagnosis ranged from immediate to several days, with the majority of diagnoses within several hours. There were seven patients with diagnoses within 12 hours, two patients between 12 and 24 hours, and one, a neonate, several days after the trauma had occurred at home secondary to child abuse.

The cause of the injuries was believed to be related to assault or trauma in four patients and iatrogenic in six patients. The injury was located in the oropharynx or hypopharynx in seven patients, and in the lower esophagus in one patient. There were two patients in whom the site of injury could not be precisely located on physical or radiographic examination.

The most common presenting symptom at diagnosis was subcutaneous emphysema, which was present in all of the patients. Radiographic studies revealed pneumomediastinum in four of nine patients (44%) and pneumothorax in one of nine (11%). Gastrografin or barium swallow studies demonstrated a leak in three of four (75%) patients.

CASE REPORTS

The following cases illustrate the methods of conservative management used.

Case 1. A 26-year-old man was admitted to the hospital after an alleged assault in which he was punched in the face and neck. On examination there was subcutaneous emphysema of the neck without hoarseness or airway distress. Indirect laryngoscopy showed edema and a laceration of the right lateral oropharynx. There was no evidence of laryngeal trauma. Plain x-ray films showed subcutaneous emphysema in the neck and a pneumomediastinum. A Gastrografin esophagogram and a computed tomography scan demonstrated cervical subcutaneous emphysema and a leak at the level of the left pyriform sinus. The patient was treated with intravenous ampicillin, gentamicin, and clindamycin for 7 days. Nasogastric feeding was discontinued and he was begun on oral feedings on the 10th day. His overall recovery was uneventful.

Case 2. A 21-year-old woman underwent an uneventful tonsillectomy under general anesthesia. The endotracheal intubation was reportedly atraumatic. On the first postoperative morning, she was found to have minimal subcutaneous emphysema of the neck at the region of the right angle of the mandible. Indirect laryngoscopy revealed normal findings. Plain x-ray films confirmed the presence of subcutaneous air. The patient was given nothing by mouth and received intravenous trimethoprim-sulfamethoxazole and metronidazole. She was discharged on the third postoperative day with a prescription for oral Bactrim.

Case 3. A 79-year-old man underwent surgery for an abdominal aortic aneurysm. On the second postoperative day, he was resuscitated following a cardiopulmonary arrest with difficult orotracheal intubation. He developed severe subcutaneous emphysema of the neck and a right-sided pneumothorax requiring a chest tube. He was extubated after 10 days of intravenous cefazolin therapy. The subcutaneous emphysema resolved and he was allowed clear liquids following extubation. He was discharged in stable condition.

Case 4. A 45-year-old man was admitted to the hospital with a 3-day history of emesis. He was a known diabetic and had alcoholic liver disease. He denied any complaints of fever, neck pain, hoarseness, dysphagia, or odynophagia at the time of admission. Following a difficult nasogastric tube placement, he was found to have subcutaneous emphysema of the neck. Indirect laryngoscopy showed edema and blood in the left pyriform sinus. Plain x-ray films confirmed the presence of subcutaneous emphysema of the neck with minimal pneumomediastinum. A Gastrografin study showed no evidence of a leak. The patient was given nothing by mouth and was treated with intravenous netilmicin and clindamycin. On the fifth day, his medication was changed to oral penicillin and he was given a clear liquid diet. He recovered without complications.

Case 5. A 57-year-old man was admitted to the hospital following a motor vehicle accident. He was unresponsive when first examined in the emergency room and was intubated with difficulty. His neurologic status subsequently improved and he was extubated after a few hours. On the following day, he was noticed to have subcutaneous emphysema of the left side of the neck and upper chest that was confirmed by plain x-ray films. Indirect laryngoscopy showed trauma to the posterior pharyngeal wall. He was given nothing by mouth for 2 days and received intravenous cefazolin and metronidazole. Clear liquids were started on the third day and antibiotics were discontinued after 1 week. He was discharged on the 10th day in good condition.

Case 6. A 39-year-old man was admitted to the hospital after sustaining fractures to the hip and ankle in a motor vehicle accident. Consultation was requested on the following day to evaluate the patient because of subcutaneous emphysema in his neck. The patient complained of neck and throat pain. He denied any hoarseness or respiratory difficulty. On examination, he had extensive subcutaneous emphysema of the neck, mainly on the left side, with extension down to the inguinal region. Indirect laryngoscopy revealed an injury to the posterior hypopharyngeal wall adjacent to the left pyriform sinus. Chest x-ray films did not show evidence of pneumothorax or pneumomediastinum, but did reveal extensive subcutaneous emphysema in the chest wall. Lateral neck x-ray films demonstrated air in the prevertebral column. The patient was treated with intravenous cefazolin and metronidazole for 1 week. A clear liquid diet was begun on the eighth hospital day. His subcutaneous emphysema slowly resolved and the hypopharyngeal injury healed without complications.

Case 7. A 45-year-old man underwent a difficult intubation for a planned direct microlaryngoscopy and excision of a vocal cord nodule. Postoperatively, the patient developed neck pain. Physical examination and neck x-ray films revealed subcutaneous emphysema. A Gastrografin swallow study revealed a right pyriform fossa leak. The patient was treated with intravenous cephalothin for 5 days with nothing by mouth, and his recovery was uneventful.

Case 8. A 92-year-old man with a 5-year history of episodes of esophageal spasm was admitted with a 5-day history of dysphagia, odynophagia, and inability to tolerate oral intake. He underwent flexible esophagoscopy by the gastrointestinal service that revealed a food bolus impaction in the lower esophagus. The service tried to remove it, but was unsuccessful. Rigid esophagoscopy to remove the foreign body and biopsy to evaluate for peptic stricture, tumor, or achalasia was performed by the otolaryngology service on the following morning and the bolus was encountered at 31 to 34 cm in the esophagus. The esophagoscope could not be passed beyond this point and biopsy specimens were taken at 31 and 33 cm. There were no discrete lesions appreciated. The patient tolerated the procedure well, but became febrile (39.0°C) and tachycardic 4 hours later. He complained of middle back pain and was tachypneic. Auscultation revealed left-sided rhonchi and rales. A chest x-ray film revealed subcutaneous emphysema and a pneumomediastinum. He had been receiving nothing by mouth postoperatively. He was given intravenous cefazolin, metronidazole, and gentamicin and was transferred to the intensive care unit for monitoring. A nasogastric tube was not placed and intravenous hyperalimentation was begun.

A barium swallow study immediately following a negative Gastrografin swallow study was performed on the third postoperative day and showed a moderate-size leak (Fig 1). Because of the patient's age and medical history, it was decided not to surgically repair the perforation. He recovered over a 3-week period and was discharged in stable condition with a gastrostomy for esophageal stricture. A follow-up esophagogram confirmed healing of the perforation prior to discharge.

Case 9. A 73-year-old woman underwent 7 to 10 unsuccessful attempts at endotracheal intubation for a planned lumbar laminectomy. The patient developed immediate subcutaneous emphysema in the

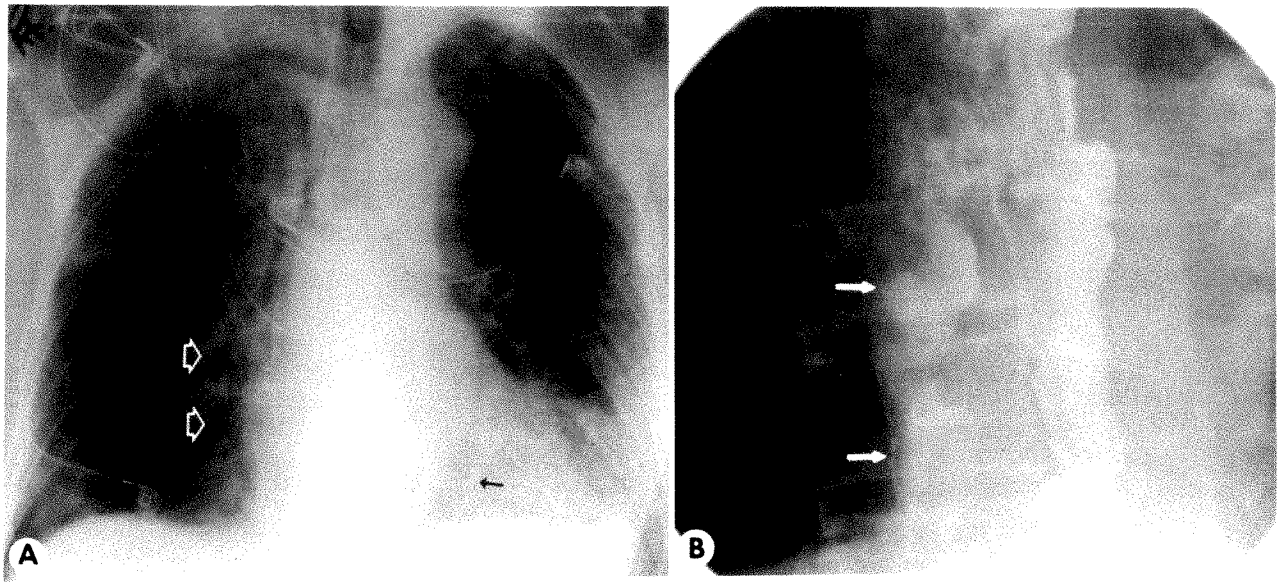

Fig 1. (Case 8) A) Chest x-ray (anteroposterior view; portable technique) showing pneumomediastinum (arrows). B) Barium swallow study revealing extravasation of contrast medium (arrows) from moderate-size, lower esophageal perforation.

neck that was greatest on the left side. Tooth 7 was fractured. The operation was canceled and the patient was observed postoperatively. She was placed on a regimen of intravenous cephalothin and penicillin G and remained afebrile. Fiberoptic laryngoscopy revealed left lateral and posterior pharyngeal wall ecchymoses. The larynx was normal. The patient tolerated a clear liquid diet begun on the following morning. Her subcutaneous emphysema was resolving. She was discharged in stable condition on the second hospital day on a 10-day course of Augmentin.

Case 10. An 18-day-old girl was admitted to the hospital for dark hematemesis that had begun that morning. Her medical history included normal gestational age with a breech delivery requiring a cesarean section. The patient was afebrile with clear, bubbling saliva in her mouth. Findings on oral, neck, and lung examinations were unremarkable; however, a chest x-ray film revealed pneumomediastinum and a lateral neck film showed free air in the lateral neck and pharyngeal soft tissues (Fig 2). A complete blood count exhibited only a moderate neutrophilia. Otolaryngology consultation was requested to evaluate the patient for a congenital branchial malformation, tracheoesophageal fistula, or injury secondary to child abuse.

The patient underwent rigid laryngoscopy and esophagoscopy. Superficial ulceration with eschar of the hard and soft palate and left tonsillar area was seen and appeared to indicate an injury several days old. It was not consistent with an injury that might have occurred at resuscitation at the time of delivery

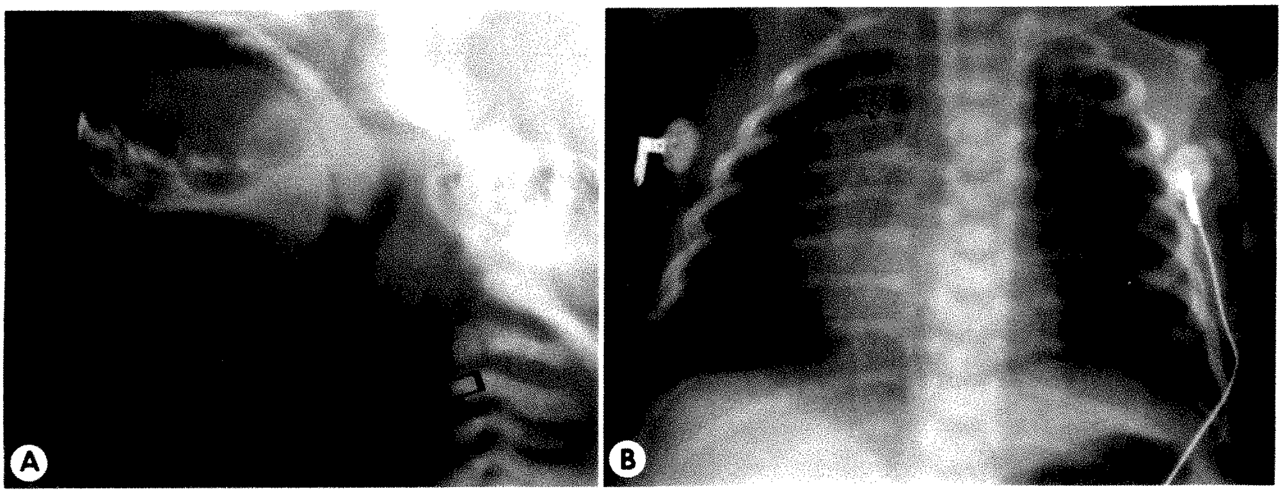

Fig 2. (Case 10) A) Soft tissue neck x-ray (lateral projection) showing free air in pharyngeal soft tissues (arrow). B) Chest x-ray (anteroposterior view; portable technique) revealing pneumomediastinum (arrow).

18 days earlier. A 1.5-cm laceration of the posterior pharyngeal wall extended down to the prevertebral fascia. Esophagoscopy showed slight edema and a 1- to 2-mm area of ulceration of the right posterolateral esophagus just above the gastroesophageal junction.

The patient was given intravenous penicillin and gentamicin and a nasogastric tube was placed. A follow-up chest x-ray film showed no increase in air on the following day. A clear liquid diet was begun on day 8. The antibiotics were converted to oral Augmentin on day 10. She was discharged home in stable condition on day 11 with visitation by the protective service after initial investigations for child abuse were negative. However, a bone scan performed on an outpatient basis 3 days after discharge was positive for healing rib fractures that were subtle and initially missed on chest x-ray films, confirming the suspicion of child abuse. This patient has had no hearing loss or other complication secondary to treatment.

No patients developed abscess formation or high elevation of temperature, other than the patient in case 8, probably because of early diagnosis and adequate treatment.

DISCUSSION

Injury to the upper aerodigestive tract can occur from penetrating or blunt trauma.[4-6,8,10] Iatrogenic injury to this region is not uncommon after endoscopic evaluation and following difficult endotracheal and nasogastric intubation.[11-13] Most reported series of pharyngoesophageal perforations involve evaluation of the injuries at different levels and are secondary to various mechanisms.[2,6] An injury secondary to instrumentation has a more favorable prognosis, because of the likelihood of earlier diagnosis and a higher location. A spontaneous perforation is usually larger and diagnosed much later, commonly involves the intrathoracic esophagus, and deeply soils the mediastinum with bacteria and gastric juices because of its explosive nature.[2,4,5,9,10] Mengoli and Klassen[1] in 1965 were among the first to advocate conservative management. They gave nonsurgical treatment to 18 of 21 cases of esophageal perforation secondary to esophagoscopy. They noted that the key to early diagnosis and prompt institution of care with intravenous antibiotic therapy and alimentation was a high index of suspicion for injury. Undue bleeding and technical difficulties during instrumentation and postoperative pain, fever, and subcutaneous emphysema led them to an early diagnosis. Chest radiography and an esophagogram further confirmed and located the injury. Their reported mortality was 6% with this approach. Of further interest is that 14 of these perforations occurred in the lower esophagus and 6 patients had an associated malignancy within the site, of which 5 healed with conservative management. Lyons et al[6] reported 9 cases of lower esophageal perforation treated successfully in a conservative fashion, of which 4 patients presented late to the hospital in a toxic state with mediastinitis and were "too sick" to withstand surgery. Wesdorp et al[4] reviewed 54 cases of instrumental esophageal perforation treated conservatively, and their findings and recommendations were similar. They recorded a mortality rate of 0% (0 of 19 patients) in perforations without associated malignancy and 8.6% (3 of 35 patients) in those with malignancy.

Blunt trauma can result from acceleration-deceleration injuries from motor vehicle accidents, blows to the neck, and strangulation injuries. A perforation of the pharyngoesophagus can result from blunt trauma to the neck when the laryngeal cartilages are compressed against the vertebral bodies. Hypertrophic, anterior osteophytes of the cervical vertebrae have been reported to cause perforation, as has hyperextension of the cervical spine with rupture of the pharyngoesophagus.[18-21]

Subcutaneous emphysema, pneumomediastinum, and pneumothorax are common manifestations of blunt and penetrating injuries to the neck and chest.[2,8] If crepitus is present following trauma, one must assume there is a tear in the aerodigestive tract. Chest and soft tissue x-ray films of the neck should be obtained to detect subcutaneous and intrathoracic air. Cervical and mediastinal emphysema can be seen radiographically in 95% of patients with cervical esophageal injuries.[19] Pneumomediastinum can be missed in about half of cases if only anteroposterior chest films are obtained. With the addition of a lateral view, nearly 100% accuracy is achieved. Pneumothorax occurs in about 50% of patients with pneumomediastinum.[20] The reliability of the Gastrografin swallow study ranges from 75% to 100%.[8] This contrast agent is water soluble and produces less reaction than barium if extravasated into the mediastinum.[5,12,21] If a repeat esophagogram is indicated, barium can be used for its higher resolution capability. A computed tomographic scan with contrast is recommended as an adjunctive study to determine the site and extent of the injury. This can direct the surgeon preoperatively if an abscess is present in the neck or in the mediastinum requiring surgical drainage. It is especially useful in a patient who is critically ill, since minimal positioning of the patient is required to perform the study.[22]

Surgical treatment consists of either primary repair of the perforation or drainage alone. According to

Hagan,[18] extensive subcutaneous or prevertebral emphysema should mandate surgical drainage. Most authorities feel that primary closure of the injury should be performed; however, this may be difficult after 24 hours because of patient deterioration and friability of the infected tissues. Tucker and Padula[23] noted that if the perforation is inaccessible and extensive dissection is necessary to ensure proper exposure, primary closure is not mandatory and simple drainage is all that is needed. There is no general agreement as to the duration of drainage. In Hagan's series,[18] drains were removed as early as the second and third postoperative days. Hagan also proposed that surgical treatment be reserved for very small (less than 1 cm) perforations with minimal subcutaneous emphysema. Complications related to upper aerodigestive tract injuries carry a 10% to 15% mortality rate. Injuries to the middle and lower portions of the esophagus appear to be more serious, with as great as a 50% morbidity and mortality rate.[10,11] The length of hospitalization and the mortality rate double in patients who receive diagnoses 24 hours after the start of symptoms.[8-10,12] Although various authors recommend direct rigid endoscopy whenever possible to evaluate the extent of the injury, we and other authors have found this not to be essential.[24,25]

Our approach differs from the protocol suggested by others. We have conservatively treated patients with extensive subcutaneous and retropharyngeal emphysema with success. The majority of our patients received diagnoses within hours. Our patient in case 8 exemplifies the success of early institution of conservative management in an elderly patient with a lower esophageal perforation who, because of age and medical history, was not an ideal surgical candidate. We believe that patients treated with a conservative protocol should be monitored closely for the development of cervical abscess or mediastinitis and, if necessary, be explored and drained surgically without delay. In the series of Shockley et al,[25] two patients treated conservatively required surgical exploration at 48 and 72 hours after initiation of antibiotic therapy. According to Loop and Groves,[26] 25% of patients treated conservatively will develop cervical abscess.

In our series, there was no uniformity as to the choice or duration of antibiotics prescribed or the use of nasogastric decompression and feeding. Proximal perforations, such as to the lateral or posterior pharyngeal wall, are less dangerous and require shorter antibiotic therapy than pyriform fossa, cricopharyngeal, or lower esophageal injuries. We currently recommend a broad-spectrum regimen of intravenous antibiotics consisting of cefazolin and metronidazole, based on the abundance of anaerobes with salivary contamination. We also use an aminoglycoside, such as gentamicin or tobramycin, for the coverage of gram-negative bacilli. Third-generation cephalosporins may be used, as well. If necessary, consultation with an infectious disease specialist should be requested. The prevalence of contamination has been reported to be increased in elderly, debilitated, and institutionalized patients, who tend to have a higher incidence of pharyngeal carriage of gram-negative bacilli.[3,21,25] Alimentation can be provided intravenously or by nasogastric tube if atraumatic passage can be obtained. However, it has been documented that the presence of a nasogastric tube can lead to increased gastric reflux and thus further contamination to the healing wound.[10] The use of follow-up Gastrografin or barium swallow studies can aid in the confirmation of closure of the injury. The duration of nothing-by-mouth status depends on the type and extent of laceration and the age and general physical condition of the patient.

CONCLUSIONS

Our experience shows that acute pharyngoesophageal injury can be managed conservatively with success. Early diagnosis is the key to the treatment of these patients, which is preferably based on a combination of intravenous antibiotic therapy and no oral feedings. Nasogastric tube decompression or alimentation has been used in some of our patients without associated complication. Mirror or fiberoptic flexible laryngoscopy was performed in nearly all of our patients to ascertain the nature of the injury. We believe that surgical drainage should be performed promptly and without delay if the patient's status deteriorates; however, none of our patients required surgical intervention. Finally, we feel that our approach has proven to be relatively safe and cost-effective, and without disability or prolonged hospitalization of our patients, although we do not have a control study to compare patients who have been surgically treated.

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THE UCSF OTOLARYNGOLOGY UPDATE: 1992

The UCSF Otolaryngology Update: 1992, will be held November 5-7, 1992, at the Ritz-Carlton Hotel in San Francisco, California. For more information, please contact the University of California, Extended Programs in Medical Education, Room LS-105, San Francisco, CA 94143-0742; telephone: (415) 476-4251.

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CRICOPHARYNGEAL MYOTOMY: INDICATIONS AND TECHNIQUE

JEFFREY A. MCKENNA, MD HERBERT H. DEDO, MD
SAN FRANCISCO, CALIFORNIA

Available diagnostic tests evaluating cricopharyngeal dysmotility are expensive, uncomfortable, and unreliable for predicting the results of cricopharyngeal myotomy. Cricopharyngeal myotomy should be performed as a diagnostic test when a patient has "block" dysphagia (in which the food bolus stops rather than the swallow's being painful) localized to the cricoid level, and when no cancer is seen on esophagram. An effective surgical technique relies on the muscular distention provided by the inflated balloon cuff of a large endotracheal tube, and requires cutting the muscle fibers of the upper esophagus, the cricopharyngeus, and the hypopharynx in the posterior midline from a point 1 cm below the cricoid cartilage to the level of the thyrohyoid membrane. The cricopharyngeal limits are indistinct until the muscle fibers have been cut. Bougies, esophagoscopes, and cuffless endotracheal tubes insufficiently distend these muscle fibers. A "peanut" sponge in a Kelly clamp is used to identify and separate the last muscle fibers from the mucosa so they can be divided. These techniques minimize the risks of esophageal perforation and incomplete muscular transection. Our experience performing 54 cricopharyngeal myotomies is reported.

KEY WORDS — achalasia, cervical dysphagia, cricopharyngeal myotomy, cricopharyngeus muscle, Zenker's diverticulum.

INTRODUCTION

Cervical "block" dysphagia is an uncommon complaint of patients seen by otolaryngologists. Anatomic causes of dysphagia such as cancer, scarring, and foreign bodies need to be excluded by physical examination, esophagram, and, in the rare case in which there is still a question, esophagoscopy. Cricopharyngeal (CP) muscle dysfunction is the most common physiologic cause of cervical block dysphagia, but it has been hard to diagnose in the past. Medical therapy for CP achalasia has been ineffective, and while CP myotomy has been shown to be effective in published clinical reports,[1-3] we now feel its indications have been unduly limited. The literature, in general, advises CP myotomy only when there is cineradiographic or manometric evidence of CP muscle dysfunction.[1] Surgeons are reluctant to operate solely on the basis of the patient's description of block dysphagia with solid foods (more so than liquids) at the cricoid level. Also, the technique usually described in the literature depends only on esophageal dilation with a bougie or esophagoscope to try to distend the muscle fibers from the lower pharynx into the upper esophagus.[4] This is ineffective and unsafe in our experience. We have found a group of patients who, when selected on a carefully taken history alone, benefit from CP myotomy even though they have "normal" cineradiographic or manometric studies. Therefore, we now advocate CP myotomy as both a diagnostic and therapeutic modality in patients with solid food block dysphagia at the level of the cricoid.

ANATOMY AND PHYSIOLOGY

The CP muscle is a sling around the junction of the hypopharynx and esophagus and is attached to the sides of the cricoid cartilage. The oblique fibers of the inferior pharyngeal constrictor blend into the CP muscle from above, as does the circular esophageal musculature from below.[5] The literature generally states that the CP muscle is in a state of tonic contraction and relaxes during deglutition. This finding was primarily based on observations made during esophagoscopy or manometry,[6] both of which stimulate mucosal stretch receptors and alter normal CP resting physiology. When the function of the CP muscle in the dog was studied electromyographically (which does not activate esophageal stretch receptors), the CP muscle was found to be relaxed in the resting state between swallows, and during each swallow it had a brief contraction-relaxation-contraction cycle.[7] Manometry in humans is uncomfortable, expensive, inconsistent, and unreliable[8] with single sensors, and can take longer than a CP myotomy; however, it occasionally has been able to demonstrate a 0.1-second delay in CP muscle relaxation in patients with block dysphagia.[9] Cineradiography, in severe cases of solid and liquid block dysphagia and in Zenker's diverticulum, has sometimes been able to demonstrate failure of proper CP relaxation during swallow.[10] In this event, the CP muscle (the "CP bar") indents the bolus of dye as it passes from the hypopharynx into the esophagus. We cannot assume, however, that if the CP muscle relaxes and opens well enough so that no bar indents the passing bolus — especially if it is only the usual liquid barium — that swallowing is normal.[8] Although the exact neurophysiologic mechanism remains controversial, it is accepted that cervical block dysphagia results from a delay or failure of relaxation of the CP muscle during deglutition.

HISTORY AND LITERATURE REVIEW

Valsalva[11] is credited with the first modern de-

From the Department of Otolaryngology–Head and Neck Surgery, University of California, San Francisco, California.

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REPRINTS — Herbert H. Dedo, MD, Dept of Otolaryngology, University of California, San Francisco, 400 Parnassus Ave, Rm 735 A, San Francisco, CA 94143.

scription of the CP region. Killian[12] in 1907 more accurately described its muscular anatomy, including the weak triangular area between the inferior constrictor and CP muscles (the site of pharyngoesophageal or Zenker's diverticulum). In 1926 Jackson and Shallow[13] suggested that CP muscle relaxation failure during deglutition causes these diverticula. Lahey[14] in 1946 recommended dilation of the CP muscle as part of the treatment of diverticulum. In 1950 Asherson[15] created the term CP achalasia, describing it as a prediverticular state.

On the basis of the theory that a dysmotile CP muscle results from bulbar or supranuclear central nervous system disorders, it was hypothesized that the surgical relaxation of the CP muscle would relieve cervical block dysphagia in patients with certain neurologic diseases. In 1951 Kaplan[16] reported the first successful myotomy in the treatment of cervical dysphagia in a patient with poliomyelitis. The efficacy of CP myotomy has since been documented,[8] in small series, for amyotrophic lateral sclerosis,[17] Parkinson's disease, cerebrovascular accidents, skull base lesions and surgery,[1] and oculopharyngeal muscular dystrophy.[18]

The usefulness of CP myotomy in head and neck cancer surgery has been recognized for over 30 years. Ogura et al[19] noted that during supraglottic laryngectomy the CP muscle was tightly constricted when the surgeon's finger was inside it, and that CP myotomy relaxed the muscle, improved deglutition, and reduced aspiration postoperatively. Mladick et al[20] and subsequent authors discussed other oncologic procedures in which CP myotomy might be included.

Cricopharyngeal achalasia may be a result of gastroesophageal reflux in some patients. In 1977 Henderson and Marryatt[21] reported on 19 patients who underwent CP myotomy, 17 of whom showed improvement. They performed a CP myotomy on patients who failed medical management of acid reflux with minimal heartburn, who were too ill for a major thoracoabdominal reflux procedure, and who had persistent dysphagia after hiatal hernia repair for reflux. In 1980 Orringer[8] reported a similar experience. Pulsion (Zenker's) diverticulum may result when normal CP function is disrupted. Konowitz and Biller[4] have recently reviewed the management of pulsion diverticulum, with emphasis on CP myotomy combined with diverticulopexy. Fundamental to their discussion is the concept that the underlying disorder is failure of the CP muscle to relax during deglutition, not a weak pharyngeal wall.

PATIENTS

Fifty-four patients underwent CP myotomy by the senior author (H.H.D.) between 1973 and 1991. Records could be obtained on 47. Follow-up was based on chart review and personal communication. Twenty-five (53%) of the patients were men and 22 (47%) were women. Patients ranged in age from 26 to 87, with a median age of 64 and an average age of 60.7. The underlying cause of the patients' CP dysfunction was not identified in 17 (36%) patients. It was identified as postlaryngectomy block dysphagia and/or failure of Blom-Singer speech in 7 (15%); cerebrovascular accident in 7 (15%); hiatal hernia with gastroesophageal reflux in 5 (11%); cranial nerve deficits from neurosurgical or skull base lesions in 8 (17%); post-hemiglossectomy status in 1 (2%); Parkinson's disease in 1 (2%); and dystonia musculorum deformans in 1 (2%). Preoperative diagnostic evaluations after indirect laryngoscopy initially included cine-esophagram, esophagoscopy (either rigid or flexible), and single sensor manometry. Seven patients had no preoperative diagnostic tests; these were in the group with multiple cranial nerve deficits (and low risk of cancer, esophageal stenosis, or Zenker's diverticulum). Of the remaining patients, 26 had an esophagram alone, and 7 had both an esophagram and esophagoscopy. Three patients had an esophagram and manometry, and 4 had esophagoscopy alone. The CP manometric studies and the esophagoscopies were unable to demonstrate CP abnormalities, so they are no longer used as diagnostic modalities for CP achalasia. Of the 36 patients who had esophagrams, only 11 patients had identifiable CP abnormalities. Three of these 11 patients had Zenker's diverticulum as a result of their CP dysfunction. The 5 patients with gastroesophageal reflux had minimal abdominal symptoms, had failed medical therapy, and had marked solid food block dysphagia at the cricoid level.

INDICATIONS FOR MYOTOMY

In the English literature on CP myotomy, the accepted indication for the procedure is the presence of a CP bar on cine-esophagram. Surgeons naturally prefer that an unequivocal diagnosis be established by a manometrist or radiologist rather than to rely on their own clinical acumen; however, manometry and cine-esophagram do not identify a group of patients whom we have found to benefit from CP myotomy. Cineradiography and manometry are not abnormal in these patients; however, the former is ordinarily performed with liquid radiopaque media when these patients have no problems with liquids. Manometry, as currently performed, uses a probe that has only a single sensor at the level of the CP muscle, which may be against the cricoid cartilage, against the upper esophageal wall during the laryngeal elevation component of deglutition, or causing reflex CP spasm. When a cine-esophagram is performed with barium-coated, chewed solid food, especially the foods that have been "catching" at the CP level, it is sometimes possible to record delay or complete obstruction at the CP muscle. Thus, when the esophagram is done properly, it may confirm that the complaint is real. Clinically useful manometry of the CP muscle awaits improved sensor technology.

In our opinion, a sufficient basis for diagnosis and surgical treatment is a careful history, and a pharyngoesophagram that shows no evidence of a cancer. This is especially true in the patient with less gross dysphagia than that causing nasal regurgitation, a Zenker's diverticulum, or a CP bar on the cine-esophagram. Patients with CP achalasia who will benefit from CP myotomy typically present with block dysphagia (bolus obstruction) at the level of the cricoid cartilage. They do not have the typical pain that accompanies those cancers large enough to cause dysphagia. They consistently have difficulty swallowing solid foods but not liquids, and require multiple attempts (often with repeated sips of water) to swallow a single bolus of chewed solid food. Nasopharyngeal reflux, laryngeal aspiration, and weight loss are seen only in severe cases. The sensation of a block is present only until the bolus of solid food passes into the esophagus, and is not present when the patient is swallowing liquids, nor between swallows (much less meals), as occurs in globus syndrome. Physical examination of the pharynx, hypopharynx, larynx, and neck is unremarkable, and a routine (liquid barium) esophagram is normal. These selection criteria identify patients with enough CP dysmotility that it should be alleviated or eliminated by CP myotomy, even though it is too subtle to be detected by cineradiography and/or manometry.

Gastroesophageal reflux is not a contraindication to performing CP myotomy in patients with solid food block dysphagia. Henderson and Marryatt[21] have reported on patients with CP achalasia who were not improved after apparent medical or surgical control of gastric acid reflux until a CP myotomy was performed. We have observed that gastroesophageal reflux symptoms have not been exacerbated by surgical relaxation of the CP muscle. Vocal cord irritation and/or granulomas have not occurred in any of these CP myotomy patients, even when followed up for years.

Cricopharyngeal myotomy is, of course, contraindicated in globus syndrome. This syndrome is characterized by a nearly constant sensation of a lump, mucus, postnasal drip, or "something stuck" at the level of the cricoid, and commonly increases or enlarges with stressful events. The syndrome has been present for months or years with fluctuation in severity (from severely annoying to absent), and does not disappear between swallows. Globus syndrome patients are easily distinguished from patients with solid food block dysphagia because the former never have difficulty swallowing liquids or solid food.

In our experience, cricoid block dysphagia patients with a history of cerebrovascular accident are suitable candidates for CP myotomy. If they have marked dysarthria, aphasia, or apraxia, however, they may have less chance of improvement. Patients with these dysfunctions may have such brain disorganization that they cannot or will not initiate a swallow.

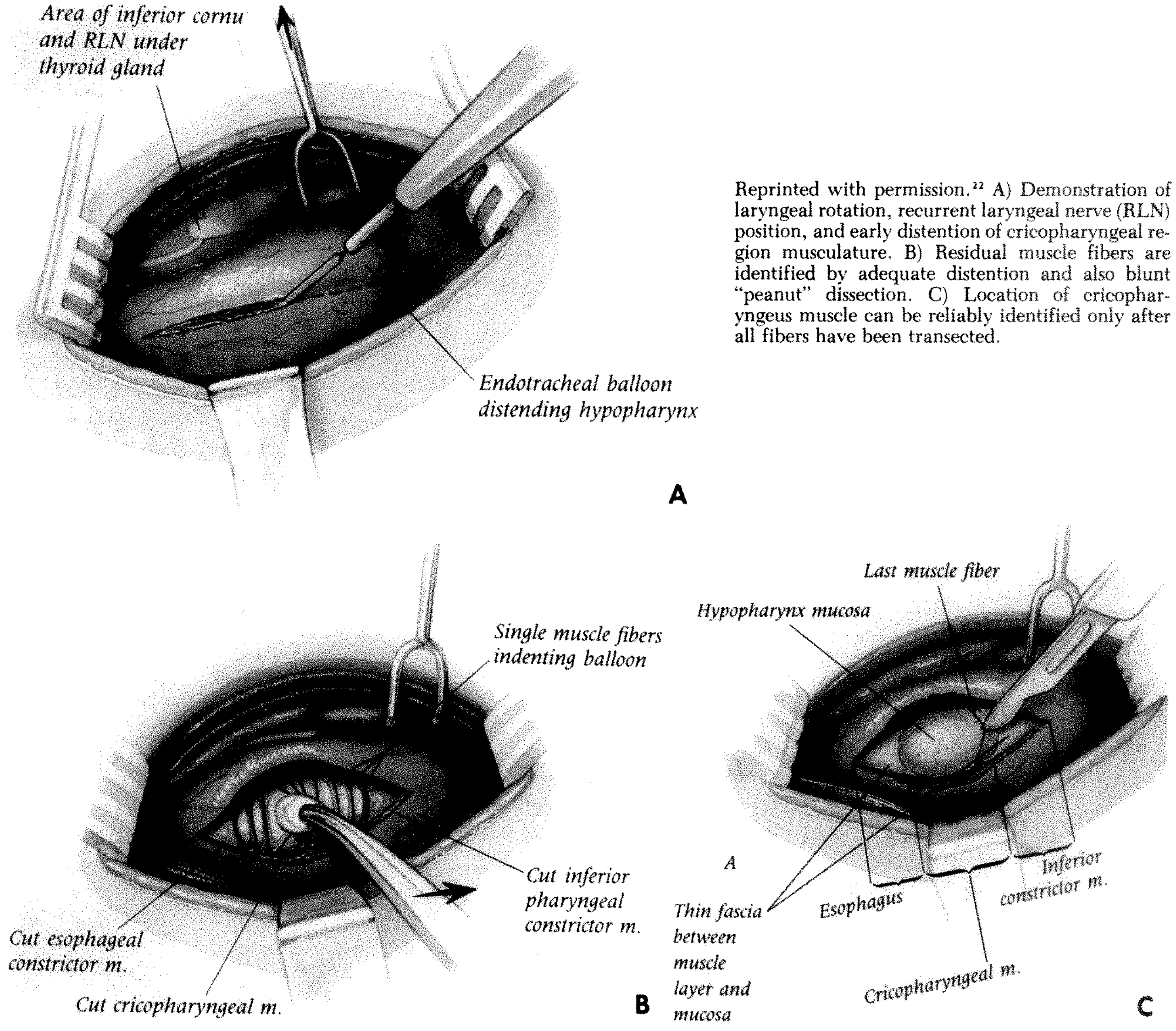
TECHNIQUE

Cricopharyngeal myotomy has a relatively low risk of morbidity and mortality. Pharyngocutaneous fistula, recurrent laryngeal nerve injury, and incomplete transection of CP muscle fibers are possible risks, but are very unlikely to occur with the following technique.

We use a standard left-sided approach to visualize the posterior surface of the CP muscle, as shown in detail in our surgical atlas.[22] The larynx is rotated away from the surgeon with a double hook on the posterior edge of the thyroid cartilage ala so that the posterior pharyngeal wall is visualized. It is important not to let the lower tine of the double hook be applied below the midpoint of the ala; it must stay well away from the recurrent laryngeal nerve, since the nerve passes behind the inferior cornu of the thyroid cartilage. For extra recurrent nerve protection, we cover the inferior cornu with the surgeon's left thumb while installing the double hook.

Distention of the pharyngoesophageal muscle fibers while they are cut is essential. Many devices have been used to try to accomplish distention, including esophagoscopes,[23] esophageal bougies or dilators,[4,8] and esophageal balloons.[24] We found that these devices do not distend the pharynx properly as the surgeon's finger does, so as to display the uncut muscle fibers, during a supraglottic laryngectomy.[19] Since there is no opening in the pharyngeal mucosa during CP myotomy, we have found that a large (36F or 38F) endotracheal tube, with a barrel-shaped, low-pressure, high-compliance cuff, is an excellent substitute for the finger because it also provides active but soft distention. We especially like this type of cuff because it distends a long segment and it does not tend to migrate into and distend only the area in which the first fibers are cut, as the older, round cuffs do. The endotracheal tube is best installed in the esophagus by the anesthesiologist after the patient is anesthetized and prior to preparing and draping the skin. If a Zenker's diverticulum is present, it will usually go into the diverticulum. Therefore, in these patients insertion is stopped as soon as the tube has been gently passed behind the cricoid cartilage and resistance is met. Otherwise, there is a potential danger of perforation. Later, when the sac has been exposed surgically and tipped upward, the anesthesiologist eases the distal end of the endotracheal tube into the upper esophagus so the balloon will be within the CP muscle.

Once the larynx is rotated and the posterior mid-


Area of inferior cornu and RLN under thyroid gland
Endotracheal balloon distending hypopharynx
A
Single muscle fibers indenting balloon
Cut inferior pharyngeal constrictor m.
Cut esophageal constrictor m.
Cut cricopharyngeal m.
B
Last muscle fiber
Hypopharynx mucosa
A
Thin fascia between muscle layer and mucosa
Esophagus
Inferior constrictor m.
Cricopharyngeal m.
C

Reprinted with permission.[22] A) Demonstration of laryngeal rotation, recurrent laryngeal nerve (RLN) position, and early distention of cricopharyngeal region musculature. B) Residual muscle fibers are identified by adequate distention and also blunt "peanut" dissection. C) Location of cricopharyngeus muscle can be reliably identified only after all fibers have been transected.

line is identified, the anesthesiologist inflates the endotracheal tube cuff (see Figure,[22] A). As the muscle fibers are cut, a distended cuff makes the uncut muscle fibers and thin submucosal fascia between the muscle and mucosal layers visually prominent because they indent the balloon (see Figure, B). A "peanut" in a Kelly clamp is used to roll uncut muscle fibers and fascia and loosen them from the underlying hypopharyngeal and esophageal mucosa prior to cutting them with a No. 15 Bard-Parker scalpel blade. During this fiber cutting, one potential pitfall is to mistake the cuff–endotracheal tube junction for an indenting muscle fiber. If the anesthesiologist deflates, moves, and reinflates the endotracheal tube cuff 1 to 2 cm caudad and cephalad after some fibers have been cut, the risk of mucosal perforation from this cause is minimized. Also, the electrocautery is used only on muscle, and not on the mucosa, to minimize risk of perforation.

Unless Zenker's diverticulum is present, we use a myotomy length of 4 to 5 cm, extending in the posterior midline from the level of the thyrohyoid membrane to 1 cm below the inferior edge of the cricoid cartilage. This cut length assures that all of the CP muscle fibers have been divided, and it has caused no postoperative problems. If there is a Zenker's diverticulum, the upper edge of the CP muscle is obvious since the inferior edge of the neck of the sac is draped over it. In this case, we tip the sac upward, position and inflate the balloon within the CP muscle, and incise its fibers in the posterior midline for 2 cm below the neck of the sac. We no longer incise over or resect the sac in order to minimize the risk of mucosal leak. It will contract down and become asymptomatic after the CP muscle obstruction is relieved,[8] especially if the thinned inferior constrictor muscle fibers are left intact on its dorsal surface. If it is larger than 3 or 4 cm, it can be rotated upward and supported with a gut suture through the inferior constrictor left on its posterior surface. Unlike the anatomy atlas illustrations, in a patient the location of the CP musculature can be reliably identified only after all the fibers have been transected, when its thickness is seen to be greater than that of the very thin esophageal muscle or the intermediate thickness of the inferior pharyngeal constrictor (see Figure, C).

RESULTS

Duration of follow-up ranged between 1 month (for 6 patients who did so well they chose not to return) and 16¾ years. The average length of follow-up was 6¼ years. The surgical outcome was evaluated clinically, since cine-esophagrams cannot demonstrate all symptomatic CP muscle dysfunction. A patient's postoperative deglutition was classified as normal, markedly improved, not improved, or worse in comparison to the preoperative state. No patient reported worsening of the symptoms by CP myotomy. Twenty-one (45%) patients reported normal swallow postoperatively. Fourteen (30%) patients reported markedly improved swallowing, but fell short of normal. (Therefore 35, or 75%, were at least markedly improved by the myotomy.) Dramatic objective evidence of improvement was that 2 patients who had required a feeding gastrostomy preoperatively were able to have the tube removed. Six (12.5%) patients had minimal improvement in symptoms, and 6 (12.5%) patients had no improvement.

Of patients without a known cause for their CP dysfunction, 15 of 17 had a markedly improved or normal swallow. Five of 7 patients who had postlaryngectomy block dysphagia had good or excellent results. In patients with cerebrovascular accidents, 6 of 7 had markedly improved deglutition. (The senior author knows of a patient, whose records were not available, who had suffered a cerebrovascular accident with resultant apraxia and dysarthria and neither improved nor worsened with CP myotomy.) Three of 5 patients with gastroesophageal reflux improved markedly. Of patients with skull base region trauma or neoplasia, only 3 of 8 had significant improvement. This finding would suggest that the presence of multiple lower cranial nerve palsies in patients who undergo CP myotomy makes improvement less likely, although the 3 patients who did improve would argue that the benefit outweighs the minimal risks of the procedure. The patients with Parkinson's disease, dystonia, and hemiglossectomy were markedly improved.

The patients were also stratified according to the duration of their follow-up. Thirty-four of the 47 patients had follow-up of 6 months or longer. Of these 34, 25 (74%) had an excellent or good surgical outcome. Only 1 had a partial recurrence of dysphagia after 6 or 7 years of marked improvement. This rate is not different from the total group improvement rate as outlined above. The patients with less than 6 months of follow-up had an improvement rate of approximately 77%. This difference is not statistically significant because of the small sample size.

Of the 36 patients who had preoperative (liquid media) esophagrams, 25 were reported as having normal anatomy and motility through the pharyngoesophageal segment, in spite of the patients' vivid description of solid food block dysphagia. Of these 25 patients, 7 (28%) had normal swallowing postoperatively, 13 (52%) had marked improvement, 2 (8%) had minimal improvement, and 3 (12%) showed no improvement. Thus, 80% of these symptomatic patients, with "normal" esophagrams preoperatively, benefited from CP myotomy, because we rejected the conventional diagnostic criteria of an abnormal liquid cine-esophagram. Also, all of the patients who had "normal" manometry preoperatively — in spite of severe clinical block dysphagia — had normal or markedly improved deglutition postoperatively.

Two patients had previously received diagnoses of CP dysfunction and had undergone myotomy by other surgeons, without improvement. After we repeated the CP myotomy using the technique described above, both patients reported that their swallowing had returned to normal. During the operation we found that they had not had a complete CP myotomy.

No patient developed vocal cord paralysis or a hematoma. One patient developed a slight wound infection, which quickly responded to antibiotics. One patient developed a small pharyngocutaneous leak on the second postoperative day, which healed spontaneously in 3 days.

SUMMARY

Deglutition is a complex neurophysiologic act. Disruption of the normal relaxation of the CP muscle during swallow results in block cervical dysphagia of solid foods, or CP achalasia. Medical treatment has not been effective. These patients' symptoms have been cured or alleviated by CP myotomy. Manometry and cineradiography are not effective in correctly identifying all of the patients who will benefit from CP myotomy. Eighty percent of these patients were markedly improved or given normal swallow by CP myotomy performed on the basis of specific symptoms described earlier, even though their cine-esophagrams and/or manometries revealed no disease. We therefore advocate CP myotomy as a diagnostic test on patients with solid food block dysphagia after excluding cancer, other anatomic lesions such as esophageal scar, and globus syndrome. Cricopharyngeal myotomy also relieves the dysphagia and lets the sac shrink when a Zenker's diverticulum is present. Gastroesophageal reflux is not a contraindication. The described technique minimizes the risks of mucosal perforation and incomplete fiber transection. The technique relies on the use of a cuffed endotracheal tube, which acts as an active muscular distention device, and creation of a myotomy of adequate length and depth to ensure complete division of the CP muscle.

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IRRADIATION-INDUCED ATHEROSCLEROSIS: A FACTOR IN THERAPEUTIC PLANNING

W. FREDERICK MCGUIRT, MD
ROBERT S. FEEHS, MD
GENE BOND, PHD
HARRIET L. STRICKLAND, DVM
WILLIAM M. MCKINNEY, MD
WINSTON-SALEM, NORTH CAROLINA

Early primary head and neck cancers (stages I and II) and occult metastatic neck disease have caused debate regarding the choice between surgery and irradiation. The arguments for each are reviewed with a new consideration: the acceleration and/or induction of carotid atherosclerosis in irradiated patients. We present clinical case reports (n = 9), a retrospective clinical evaluation for the occurrence of carotid atherosclerosis in irradiated head and neck cancer patients (n = 57), and a comparison study of the extent and distribution of atherosclerosis in irradiated (n = 29) and nonirradiated head and neck cancer patients controlled for age, blood pressure, and tobacco use. The results show that carotid atherosclerosis is found in a wider anatomic distribution and to a greater extent in irradiated than in nonirradiated patients. We conclude that carotid atherosclerosis is induced and/or accelerated by neck irradiation. The implications as they relate to choice of treatment, to pretreatment evaluations, and to long-term follow-up are discussed.

KEY WORDS — carotid atherosclerosis, carotid ultrasound, head and neck neoplasms, irradiation.

INTRODUCTION

The proper treatment of the N0 neck remains an unresolved issue. Whether initial treatment of the neck concomitant with treatment of the primary tumor is beneficial and, if it is, which are the preferred method and proper timing remain debatable. Prevailing opinions are 1) that neck disease should be addressed when the expected occult rate exceeds 20%, and 2) that the neck may be treated equally well by irradiation or surgical dissection.[1,2] Similarly, because many T1- and T2-staged primary head and neck tumors have cure rates from either surgery or irradiation that are essentially equal, the same quandary as to the preferred treatment modality remains.

When different therapeutic modalities yield comparable results, the choice must be based on other variables. Important questions that must be addressed before treating occult metastatic nodal neck disease are

1. Is the primary tumor to be treated by surgery alone, or will irradiation, alone or as part of combined therapy, be used?
2. If surgery is to be used, will the approach be through the neck and allow simultaneous management of occult nodal disease?

Secondary considerations include

1. Is the primary tumor at the midline, requiring treatment to both sides of the neck?
2. Would a modified neck dissection limit the size of the irradiation field and thus the morbidity of irradiation?

With the myriad of opinions and data sources available, there is still no agreement between those preferring surgery and those preferring irradiation for occult metastatic or small primary tumors of the upper aerodigestive tract.[3-16]

Barring relevant social and economic considerations, the crucial medical question is that if both modalities of treatment are equally efficacious in the same disease setting, then which of the two causes the least harm or risk to the patient? Historically, negative surgical considerations have included loss of function,[17] cosmesis, and anesthetic and metabolic risks. Cosmesis and function are lesser factors now, since conservation and selective regional neck dissections have become the standard of care for occult disease.[3,18] Negative considerations for radiotherapy have included hypothyroidism,[19] xerostomia,[20-24] dental sequelae,[25] and loss of future treatment options for subsequent second primaries in patients at high risk for metachronous lesions.[26] What we believe now to be an additional major negative consideration relevant to the use of irradiation has been identified and prompts this report. This negative factor is the effect of irradiation on the carotid artery.

STUDY DESIGN AND RESULTS

We became concerned about this problem when we realized that nine of our head and neck cancer

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From the Department of Otolaryngology (McGuirt, Feehs), the Department of Neurobiology and Anatomy, Division of Vascular Ultrasound Research (Bond, Strickland), and the Department of Neurology (McKinney), The Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina.

Presented at the meeting of the American Laryngological Association, Waikoloa, Hawaii, May 4-5, 1991.

REPRINTS — W. Frederick McGuirt, MD, Dept of Otolaryngology, Bowman Gray School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157.

TABLE 1. RESULTS OF DIAGNOSTIC MEDICAL ULTRASOUND IN PATIENTS WITH HEAD AND NECK TUMORS HAVING UNDERGONE RADIOTHERAPY

Pt No.	*Sex*	*Left/Right*			*Stenosis*
		CCA	*BIF*	*ICA*	
1	M	0/0	1/0	0/0	
2	M	1/0	1/0	1/0	
3	F	1/1	1/1	2/1	
4	F	1/0	1/2	1/0	
5	M	1/0	3/2	3/2	Decreased flow
6	M	NE	2/1	1/2	
7	M	1/1	1/2	2/2	
8	F	0/0	0/2	0/0	
9	M	1/0	2/2	3/3	Occlusion R; 50%-75% L
10	M	1/2	3/3	3/2	Occlusion ICA L; stenosis R
11	F	0/0	0/0	0/0	
12	F	1/2	1/0	1/1	
13	M	1/1	0/1	2/0	
14	F	0/1	1/2	1/2	
15	M	2/1	2/1	1/2	
16	M	1/1	1/3	2/2	Yes; 50%-75% L
17	F	0/0	1/1	0/0	
18	M	1/1	2/1	2/2	Yes; 50%-75% L
19	M	0/0	1/2	0/0	Yes
20	M	1/1	2/2	0/0	Yes
21	M	1/0	0/2	1/1	
22	F	0/0	2/2	2/2	Yes; ICA 1.4 mm R
23	M	2/1	2/1	2/2	Yes; 75%-95% L
24	M	2/1	2/0	2/1	Yes; 75%-95% bilaterally
25	M	0/0	1/2	0/0	
26	M	0/1	0/2	1/0	
27	F	0/1	1/2	1/2	
28	M	2/1	1/1	1/1	
29	F	1/0	2/1	2/0	
30	F	1/0	2/2	1/1	
31	M	1/0	1/0	2/1	
32	M	1/0	0/0	0/0	
33	M	1/2	2/2	0/1	
34	M	0/0	0/1	0/0	
35	M	1/2	2/2	1/2	
36	F	1/0	1/1	1/0	
37	F	2/0	2/2	1/2	
38	M	0/0	2/1	2/0	
39	M	1/2	1/3	2/2	
40	M	0/0	2/2	1/2	
41	F	0/0	2/1	0/1	
42	M	1/1	2/2	2/2	
43	F	1/2	0/0	0/2	
44	M	1/1	2/2	2/3	Yes; 50%-75%
45	M	0/0	1/0	3/0	
46	F	0/2	1/1	0/1	
47	M	1/2	2/2	2/2	
48	M	2/1	1/1	1/0	
49	M	?/3	3/3	ND	Occluded system R
50	M	1/1	1/2	2/1	
51	M	2/2	?/2	?/2	
52	M	1/0	0/2	0/0	
53	M	2/2	2/2	2/0	Minimal flow R
54	M	2/1	1/2	0/1	
55	M	0/0	0/0	1/0	
56	M	2/?	2/?	2/?	
57	M	0/0	0/1	0/0	

0 — none, 1 — minimal plaque, 2 — moderate plaque, 3 — large plaque, CCA — common carotid artery, BIF — bifurcation, ICA — internal carotid artery, NE — not examined, ND — no flow detected.

TABLE 2. SUMMARY OF STUDY GROUP 1

	No. Pts	*%*
Plaque severity		
Grade 0	1	1.75
Grade 1	8	14.0
Grade 2	40	70.1
Grade 3	8	14.0
Stenosis	13	22.8
Plaque distribution		
Bifurcation	53/57	93.0
Internal carotid artery	46/57	80.7
Common carotid artery	45/57	78.9

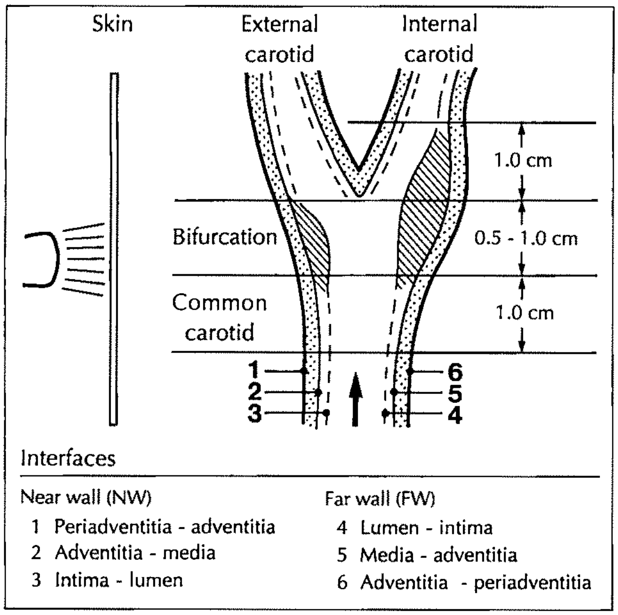
0 — none, 1 — minimal plaque, 2 — moderate plaque, 3 — large plaque.

patients had reported symptoms compatible with, and on workup ascribed to, carotid vascular disease. Summaries are presented in Case Reports. All patients had been treated with neck irradiation alone or in combination with surgery. Once alerted to the possibility of accelerated atherosclerosis following irradiation in head and neck cancer patients, we evaluated this hypothesis further.

Initially, 57 patients (study group 1) who had received neck irradiation as part or all of their treatment were randomly selected from those seen in our head and neck tumor clinic. These patients were referred to the Bowman Gray School of Medicine clinical ultrasound neurosonology laboratory for carotid artery evaluations. Real-time analysis was done on a Biosound Phase 2 machine. Three views (anterior, lateral, posterior) of each carotid artery were imaged. The posterior view was used to measure plaque thickness, because it best correlates with the arteriographic lateral view. Plaque thickness was measured to within 0.1-mm confidence and recorded for the common, internal, and external carotid arteries, as well as the bifurcations. The degree of plaque deposition or formation was reported as none, minimal (1 to 2 mm), moderate (2.1 to 4 mm), or large (>4 mm).

The results are given in Tables 1 and 2. A marked preponderance of patients (48 of 57 or 84.2%) had moderate to severe carotid atherosclerosis. Plaque deposition was greatest at the bifurcation (53 of 57 or 93.0%). The internal carotid (46 of 57 or 80.7%) and common carotid vessels (45 of 57 or 78.9%) of most patients had atherosclerotic changes as well. This unexpected finding was contrary to historical institutional data, which indicated that while the preponderance of atherosclerosis occurred at the carotid bifurcation, only rarely was it seen in the common and internal carotid systems.[27] In addition, 13 of 57 (22.8%) patients had stenosis of at least 50% and/or flow reductions noted by Doppler measurements. These ultrasound findings supported our original clinical observations and our concern that irradiation of the neck might accelerate or induce carotid artery atherosclerosis.

Because the initial study group had not been



Schematic of high-resolution B-mode ultrasonograph of right carotid artery with lesion in bifurcation. Near wall interfaces (1, 2, and 3), and far wall interfaces (4, 5, and 6) are identified. (Reproduced with permission from Feehs RS, McGuirt WF, Bond MG, Strickland HL, Craven TE, Hiltbrand JB. Irradiation. A significant risk factor for carotid atherosclerosis. Arch Otolaryngol Head Neck Surg 1991;117:1135-7.)

compared with nonirradiated patients, and because no risk factors other than irradiation had been considered, 29 additional head and neck cancer patients (study group 2) who received therapeutic irradiation as all or part of their therapy were randomly selected for study in the laboratory of the Division of Vascular Ultrasound Research. These patients were compared with nonirradiated head and neck cancer patients also randomly selected from the same tumor registry. These control patients were comparable to an institutional stroke center data bank control population.

All test patients had received radiotherapy at least 3 years before the study. Each patient underwent B-mode ultrasound carotid examinations using the Biosound 2000 IIs.a. (8-MHz transducer) unit, which measures plaque thickness to within 0.1-mm confidence. Maximal intimal-medial arterial wall thicknesses were measured in the distal common carotid artery (CCA), the proximal internal carotid artery (ICA), and the carotid bifurcation (see Figure). An atherosclerotic plaque was defined as being present when the intimal-medial thickness was greater than 1.3 mm and was accompanied by nonparallel displacement of the interfaces used to define the intima and media. To obtain a value indicative of a patient's overall carotid intimal-medial thickening, the means for the near and far walls were averaged to yield a single mean maximal score. Age, blood pressure, tobacco consumption, and plasma cholesterol were recorded and compared for the two groups, as were the mean intimal-medial wall thickness and the distribution of plaques.

TABLE 3. SUMMARY OF STUDY GROUP 2

	Test	*Control*	*p*
Plaque severity as measured by mean maximal intimal-medial thickness (mm)			
Mean	1.28	0.90	.003*
SE	0.06	0.05	
Range	0.55-1.97	0.70-1.13	
Plaque incidence (% patients)	93	67	
Location of plaques (% patients)			.0007†
Bifurcation	89	100	
Internal carotid artery	63	0	
Common carotid artery	63	0	
Risk factors other than irradiation (mean ± SE)			
Age (y)	62.6 ± 11.6	58.7 ± 13.8	.40§
Systolic blood pressure (mm Hg)	138.6 ± 18.5	128.3 ± 20.7	.21§
Tobacco (pack years)	42.9 ± 28.7	50.5 ± 32.0	.32§

*Student's *t* test.

†Fisher's exact test.

§Analysis of covariance.

Statistical comparison between the two groups showed significantly more severe and more extensive atherosclerosis in the irradiated group (range, 0.55 to 1.97 mm; mean ± SE, 1.28 ± 0.06 mm) than in the control group (range, 0.70 to 1.13 mm; mean ± SE, 0.90 ± 0.05 mm). By Student's *t* test, these differences were statistically significant at the $p = .003$ level (Table 3), and they remained statistically significant (analysis of covariance) after possible confounding effects such as age, blood pressure, and tobacco consumption had been examined (Table 3). No patient in either group was hypercholesterolemic.

Intimal-medial thickening greater than 1.3 mm (plaque) was present in 93% of the irradiated patients and 67% of controls. Plaques were located at multiple sites in 81% of irradiated patients, with 33% of the patients having plaques in all three arterial segments. Control patients, however, had plaque involving only the carotid bifurcation. These differences in plaque distribution among arterial segments were significant ($p = .0007$, Fisher's exact test; Table 3).

Our conclusion was, as we had suspected clinically, that irradiation contributes to the development of more severe and more extensive carotid artery atherosclerosis in head and neck tumor patients.

CASE REPORTS

Patient 1 was a 70-year-old man with a T2N3M0 nasopharyngeal carcinoma. He had full-course radiotherapy to the primary lesion and both sides of the neck (60 Gy). Ten years later he developed episodes of right-sided numbness or weakness and syncopal attacks, and had three episodes of amaurosis fugax in the left ear. Carotid artery duplex ultrasound revealed a left internal carotid occlusion of 90% and a plaque with 40% occlusion of the right bifurcation and ICA. He was treated medically.

Patient 2 was a 76-year-old woman with a T2N0M0 tongue base carcinoma. In 1978, she received full-course radiotherapy to her primary lesion (65 Gy) and both sides of the neck (50 Gy). A second head and neck primary lesion was diagnosed in May 1984. Carotid ultrasound was performed because of carotid bruits heard bilaterally on physical examination. A right-sided CCA stenosis of 50% to 70% and a left-sided ICA stenosis of 50% to 75% were reported. The patient died of her second cancer before the carotid problem could be addressed.

Patient 3 was a 73-year-old man with a tongue base T1N0M0 carcinoma. He was treated with radiotherapy (60 Gy to the primary lesion and 50 Gy to both sides of the neck). Nine years later he developed syncopal episodes and transient ischemic attacks. An arteriogram showed bilateral plaques with 50% stenosis of the left CCA. Carotid endarterectomy was performed.

Patient 4 was a 74-year-old man who presented with a T2N0M0 supraglottic carcinoma of the larynx that was treated with preoperative radiotherapy (45 Gy to the left side of the neck and 20 Gy to the right side of the neck). Eighteen years later he presented with a second primary lesion and a 2-year history of transient ischemic attacks. Carotid arteriograms indicated right carotid obstruction, and ultrasound confirmed no flow in the right ICA and a 50% to 75% stenosis in the left ICA. The patient was treated medically.

Patient 5 was a 68-year-old man with T3N0M0 carcinoma of the right tonsil. He was treated with 68 Gy to his primary lesion. Two years later he was admitted with second and third primary lesions. Seizures developed after laser resection of a postpharyngeal lesion. A 95% stenosis of the right CCA and ICA and 75% occlusion of the left CCA and ICA were found on carotid ultrasound during the workup of his seizure.

Patient 6 was an 87-year-old man with T2N0M0 laryngeal cancer who was treated with 68 Gy to the primary lesion and 50 Gy to both sides of the neck. Later, a metastatic node appeared within the irradiation portal and a radical neck dissection was performed. Two years after the initial irradiation treatment, the patient began having syncopal episodes and was noted to have bilateral carotid bruits. Carotid Doppler studies revealed 40% ICA stenosis bilaterally with a calcified plaque being noted in the bifurcation. He was treated medically.

Patient 7 was a 60-year-old man with a T2N1M0 carcinoma of the oropharynx who received radiotherapy with 60 Gy to the primary lesion and 50 Gy to both sides of the neck. Three years posttherapy the patient began having episodes of dizziness and blurred vision. A workup revealed a 95% occlusion of the left CCA and bifurcation and a 75% stenosis of the right ICA. He was treated medically.

Patient 8 was a 65-year-old woman who was treated with 53 Gy to the neck following a radical neck dissection for a delayed-appearing neck metastasis from a T1 mobile tongue lesion. She developed a second primary 7 years later, requiring a mandibulectomy. Seven and a half years following irradiation, the patient had a right temporoparietal cerebrovascular accident with left hemiparesis. Doppler ultrasound revealed a moderate plaque in the right ICA and a minimal plaque at the bifurcation and the CCA. Atherosclerosis was seen at the bifurcation.

Patient 9 was a 59-year-old woman who had excision of an adenoid cystic carcinoma of the floor of the mouth and a radical neck dissection. Postoperatively, she received 54 Gy to the primary site and 41.4 Gy bilaterally to the neck. Thirty months later she complained of dizziness on turning her head. A carotid Doppler scan revealed a moderate plaque at the carotid bifurcation and a severe plaque at the internal carotid origins. Medical therapy was instituted.

DISCUSSION

Radiotherapy plays a prominent role in the treatment of head and neck cancer. Its use is well established in the curative treatment of subclinical cervical node metastases, in the management of small primary mucosal tumors, and in combination with surgery for the eradication of manifest cervical node metastases and many larger primary tumors.[28-30]

Similarly well established by animal studies and anecdotal human observations are changes within the vascular system — intimal thickening, lipoid deposition, and adventitial fibrosis — that follow external irradiation to other parts of the body. All these changes, seen in arteriosclerosis and with the normal aging process, are produced or accelerated by irradiation.[31-35] Over long periods of survival, low doses of radiation (25 Gy) cause these same vascular changes and cause them to the same degree as doses higher than 45 Gy.[36] Irradiation-induced coronary artery disease in nonatherosclerotic young women and young men following chest and mediastinal irradiation has been reported[37-41]; ie, these changes may occur in the vessels of patients without preexisting atherosclerotic changes and in whom atherosclerosis is not normally seen.

Although the carotid vascular system is included in the treatment portals for irradiation of head and neck cancers, previous reports of irradiation damage to these large arteries are few[42-45] and are found predominantly in neurosurgical and vascular surgical journals.[46-49] The paucity of information on this subject directed toward head and neck oncologists has masked the magnitude of the problem and delayed awareness that accelerated atherosclerosis from irradiation to the neck is not uncommon. Further contributing factors to this low level of awareness are the high mortality from the primary disease or other concomitant diseases in this elderly population, and the fact that these complications are treated by neurovascular medical and surgical specialists rather than by the head and neck oncologic surgery team.

Furthermore, most head and neck cancer patients are treated in the later decades of life and have been heavy smokers — both major historical correlates to vascular disease that may have previously masked recognition of the atherosclerotic effect of irradiation. The acceleration of the atherosclerotic process by carotid irradiation to the point of vascular insufficiency and neurologic sequelae or even to the end result of vascular obliteration, while not documented sequentially by these retrospective and comparative studies, should be suspected from the data reported. The case reports given here and the high incidence of significant stenosis in our retrospective uncontrolled clinical ultrasound study group 1 lend support to this concept. Our 22.8% incidence of hemodynamically significant lesions is in keeping with that of two other retrospective studies: one by Scholz et al,[50] comprising 37 patients having a 19% incidence, and one by Elerding et al,[51] comprising 118 patients having a 25% incidence. Compared with a 2.7% incidence in 556 controls in the study by Scholz et al, our findings and others represent a tenfold increase of hemodynamically significant lesions in the irradiated patient groups. Elerding et al noted a twofold increase in stroke incidence in comparison to their controls.

The studies of Scholz et al and Elerding et al and our case studies and study group 1 correlated the presence of carotid stenosis and prior irradiation. Our study group 1 in addition indicated a distribution and severity of carotid atherosclerosis not previously recognized. These studies did not, though, evaluate the significance of irradiation as a risk factor in relation to other known risk factors for atherosclerosis. Therefore, we undertook the comparative study of irradiated and nonirradiated patients comparing other risk factors. Data from this second study confirmed a statistically significant difference in the degree and distribution of carotid artery atherosclerosis within the test and control groups. The only causative differentiating factor was that the test group patients had received irradiation to the neck. The other factors known to be associated with atherosclerosis, such as hypertension, age, and tobacco use, were not statistically different between the two groups (Table 2).

This acceleration and worsening of atherosclerosis by irradiation should be a real concern, especially when treating patients with any history or physical findings of pretreatment diffuse arteriosclerosis. Awareness of this problem should dictate caution in incorporating neck irradiation into the treatment protocols of head and neck cancer patients. Both older patients with preexisting vascular disease and younger patients with longer life expectancy are at risk for progressive obliterative effects of radiotherapy. Such patients may be better served by alternative protocols excluding irradiation if the cure rates are comparable.

The above conclusion is particularly true for the patient with an N0 neck, in whom a conservative neck dissection or even observation and subsequent neck dissection[4,7] for later-manifested disease might be equally effective. In patients with manifest nodal disease confined within the nodal capsule, a neck dissection alone has proved to be sufficient therapy.[52] Similarly, for hypopharyngeal carcinoma, combined therapy has been questioned as to increasing survival beyond that of surgery alone.[53,54] A true increased benefit must be shown before the irradiation arm of therapy is routinely added to or replaces surgery.

All head and neck patients for whom irradiation is an option for treatment should be considered for a carotid ultrasound study as part of their pretreatment workup. Identification of carotid vascular disease and the risk of exacerbating this disease by irradiation must be weighed against a documented enhancement of cure by the inclusion of irradiation. For those patients who require neck irradiation, sequential carotid evaluations and a search for early clinical symptoms that would evoke interventional therapy should be performed. In non–high-risk patients, a clinically heightened suspicion should dictate when carotid vascular studies are appropriate.

The purpose of this communication is to alert the head and neck oncologist to the potentially serious side effect of accelerated atherosclerosis following irradiation in patients with head and neck cancer.

CONCLUSION

As suspected by clinical observations, ultrasonographic evaluation confirms that irradiation contributes to the development of severe and extensive carotid artery atherosclerosis in head and neck tumor patients.

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CONGENITAL LACK OF OLFACTORY ABILITY

DONALD A. LEOPOLD, MD
BALTIMORE, MARYLAND

DAVID E. HORNUNG, PHD
SYRACUSE, NEW YORK

JAMES E. SCHWOB, MD, PHD
SYRACUSE, NEW YORK

Twenty-two patients, all of whom reported never having been able to smell anything, were studied to determine the particular features that distinguish individuals with congenital anosmia. The clinical evaluation on these patients included a thorough medical and chemosensory history, physical examination, nasal endoscopy, chemosensory testing, olfactory biopsies, and imaging studies. There was no evidence to indicate that these patients ever had a sense of smell. The results of olfactory testing suggested that these patients had an inability to detect both olfactory and trigeminal odorants; however, many of the patients in the group seemed to have a slight ability to perceive at least some component of trigeminal odorants. The olfactory epithelium, if it was present at all on biopsy, was abnormal in appearance.

KEY WORDS — choanal atresia, congenital anosmia, diagnostic imaging, human genetics, hypogonadism, odors, olfaction, olfactory bulb, olfactory mucosa, smell.

Among patients who complain of a poor sense of smell, there is a small but discrete group who say that they have never smelled anything. Because these patients have never experienced an odor sensation, they are said to have a congenital lack of olfactory ability. These individuals have a difficult time understanding the concept of odor and have developed alternate mechanisms for dealing with food, fragrances, and volatile chemicals.

Congenital anosmia is a poorly understood entity from the standpoint of categorization, heredity, or pathophysiology. For purposes of discussion, two broad categories are often considered: congenital anosmia that occurs in concert with other anomalies, and congenital anosmia that occurs as an isolated condition. Congenital anosmia that occurs in association with other anomalies has been recognized for many years. Perhaps the most notable example is Kallmann's syndrome — hypogonadotropic hypogonadism accompanied by total anosmia. Congenital anosmia has also been associated with premature baldness and vascular headaches,[1] choanal atresia,[2] alopecia universalis,[3] ichthyosis and hypogonadism,[4,5] and congenital insensitivity to pain.[6]

The purpose of this paper is to describe the clinical presentation of these patients, discuss how their chemosensory status can be evaluated, illustrate the histopathologic changes in their olfactory mucosa, and determine if the absent olfactory ability is accompanied by other anomalies. Methods of management of patients who have a congenital lack of olfactory ability will also be discussed, as will strategies as to how patients might use nonolfactory cues to cope with this congenital defect.

MATERIALS AND METHODS

The material for the present report comes from 22 patients (14 female, mean age 34 years, range 14 to 58; 8 male, mean age 22, range 14 to 35) with a congenital lack of olfactory ability. These patients were evaluated at the Clinical Olfactory Research Center of the SUNY Health Science Center in Syracuse, New York, from 1984 through 1990. As described below, a detailed history of these patients' chemosensory status was obtained. A head and neck physical examination was then performed, with special attention to the patency of the upper nasal cavities and character of the nasal mucosa. In 18 of these patients, the nasal and sinus cavities were imaged by computed tomography (CT). The olfactory abilities were measured in 19 of the patients, and in 5 of the patients, biopsy specimens of the olfactory epithelium were obtained by using the techniques originally described by Lovell et al.[7]

History. Since there is no known method of positively identifying someone as having a congenital lack of olfactory ability (eg, with a blood test or biopsy), the diagnosis must be made from the patient's history and the lack of any alternative explanation for the anosmia based on the physical examination. Because congenital anosmia is to some extent a diagnosis of exclusion, it was essential that each patient's history be explored in an orderly fashion, with a careful physical examination including all of the features that are discussed below.

The diagnosis of a congenital lack of olfactory ability was suggested when the patient indicated

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From the Departments of Otolaryngology (Leopold), Physiology (Hornung), and Anatomy and Cell Biology (Schwob) and the Clinical Olfactory Research Center (all authors), State University of New York Health Science Center, Syracuse, New York. Supported by National Institutes of Health/National Institute on Deafness and Other Communication Disorders grant 9-P01 DC00220.

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REPRINTS — Donald A. Leopold, MD, Johns Hopkins Dept of Otolaryngology–Head and Neck Surgery, Francis Scott Key Medical Center, 4940 Eastern Ave, Baltimore, MD 21224.

that he or she had never had a sense of smell.[8,9] However, even with this admission, it was necessary to eliminate other causes for the olfactory deficit by asking questions about head trauma, nasal disease, upper respiratory tract infections, etc. Because patients who have lost their olfactory abilities before the age of 6 often do not remember ever having had a sense of smell, they and their parents (if possible) were thoroughly questioned about any head trauma or major respiratory tract infections that might have occurred during early childhood. Since virtually everyone has upper respiratory tract infections as a child, and since childhood trauma is also a relatively common event, eliminating these as causative agents for the olfactory deficit was difficult. A behavioral or eating pattern change that followed a head injury or respiratory infection suggested the possibility of an olfactory sense that was lost during early childhood, and therefore these patients were not classified as congenitally anosmic. In addition, the knowledge that occipital blows are more likely to cause olfactory loss helped in this judgment.

To evaluate for the endocrinologic problems that are sometimes associated with a congenital lack of olfactory ability (such as hypogonadotropic hypogonadism), inquiries were made regarding sexual development. In both sexes, questions regarding adult body development, the distribution of axillary and pubic hair, and fertility were particularly important.

Between the ages of 5 and 10, many patients with a congenital lack of olfactory ability began to realize that friends and family members perceived something called odors, which they could not perceive. Commonly cited odorants that were not perceived included freshly prepared popcorn or a recently discovered skunk. The patients soon learned to "play along," and acted as if the odor could be recognized so that they would not be thought of as being different. With the maturity that accompanies the midteen years, patients usually began to discuss this problem with family members or close friends. In many instances, the nature and severity of the problem were not appreciated or understood. Consultation with physician(s) usually resulted in laboratory or imaging studies; however, abnormalities are infrequently found and a satisfactory understanding of the reason for the poor olfactory ability was often not obtained.

Patients with this congenital lack of olfactory ability usually discovered that they could successfully function in the olfactory world by fastidiously cleaning themselves and their surroundings. They used little or no fragrance for fear of applying too much. Freshly opened foods were labeled and discarded after a few days to avoid the possibility of spoilage. It was soon learned that lumpy milk and green bologna resulted in gastrointestinal discomfort. Many solicited the assistance of friends or family members in matters of smell.

Since these patients could not detect the aroma of food, they often emphasized factors such as texture, color, and the presence of only a sweet, sour, salty, or bitter taste when describing what they ate. For example, to appreciate the crispness of the flakes, some patients ate cereal without milk. Similarly, foods with a soft texture, such as guacamole and tapioca pudding, were often disliked.

Physical Examinations, Imaging Studies, and Biopsies. The physical examination for a patient with congenital anosmia is important in identifying abnormalities such as nasal disease, which could change the patient's diagnosis and treatment. Accordingly, during the examination, the patency of the nasal airways in the region leading up to the olfactory clefts was determined. Although this was most easily accomplished with the aid of an endoscope, conditions like choanal atresia were diagnosed with the aid of a CT scan. To completely eliminate the possibility that the olfactory deficit occurred as a result of nasal obstructive disease, it was necessary that the nasal cavity be patent the day the olfactory testing was performed.

The physical examination is also important in identifying anomalies that are sometimes associated with congenital anosmia and that may need treatment. For example, it was essential to check for the presence of endocrinologic problems,[2] midline facial defects,[10] alopecia,[3] vascular headaches,[1] ichthyosis,[4,5] and congenital insensitivity to pain.[6]

Chemosensory Testing. The olfactory ability was assessed by the patient's performance on the Odorant Confusion Matrix (OCM).[11] In this test, 10 single chemical odorants were presented to the patient in random order. After smelling each odorant, the patient chose a word from a closed set of 10 words that best described the odor that was smelled. The block of 10 odorants, in random order, was then repeated 9 more times until 10 blocks had been presented. These 100 presentations and responses were then recorded in a matrix (Table 1) that showed not only the correct responses along the diagonal, but also the pattern of incorrect substitutions. Since the subject had 10 choices for each stimulus, the chance performance level for this test was 10% correct.

From a preliminary analysis of the OCM results, it became apparent that the olfactory ability of the congenitally anosmic patients was poor at best, approaching chance performance in many patients. Because of this olfactory deficit, there was at least the possibility that patients would respond with the same word to a number of different odorants. This response bias could confound an odor-by-odor analysis of the OCM percent correct score. At the extreme, consider a patient who responded with "rose" to each of the 100 stimuli. Since rose was cor-

TABLE 1. ODORANT CONFUSION MATRIX SHOWING NUMBER OF RESPONSES

	Ammonia	*Cinnamon*	*Licorice*	*Mint*	*Mothballs*	*Orange*	*Rose*	*Rubbing Alcohol*	*Vanilla*	*Vinegar*
Ammonia	1	1	1	—	1	2	1	1	—	2
Cinnamon	—	1	—	1	1	2	—	—	5	—
Licorice	—	1	—	1	1	—	1	1	5	—
Mint	—	—	1	2	—	1	1	—	5	—
Mothballs	1	—	1	3	1	—	—	1	3	—
Orange	—	2	—	—	2	—	1	1	3	1
Rose	—	—	1	1	—	—	2	1	5	—
Rubbing alcohol	—	—	1	2	—	—	—	3	4	—
Vanilla	—	1	1	—	1	—	—	2	5	—
Vinegar	5	—	—	—	—	—	—	1	—	4
Column totals	7	6	6	10	7	5	6	11	35	7

This matrix shows olfactory test results on one congenitally anosmic patient. Odorant stimuli are listed along left side, and patient's responses are in columns under appropriate odorant name. For 10 vinegar trials, this patient responded with name "ammonia" 5 times, "rubbing alcohol" once, and "vinegar" 4 times. Since this patient correctly identified vinegar 4 out of 10 times, odorant confusion matrix score for vinegar was 40% correct. Diagonal from upper left to lower right contains number of correct responses for each stimulus. Diagonal total for all 10 odorants was 19; thus, for 100 presented odorants, this patient scored 19% correct. Column totals represent number of times patient chose each odorant name. Notice large number of times (35) patient responded with word "vanilla."

rectly identified all 10 times it was presented, the percent correct for rose would be 100%. On the other hand, the percent correct for the other 9 odorants on the OCM would be zero. Clearly, in this example the percent correct for rose is inflated by the response bias of the patient. Although this is an extreme example, one of the congenitally anosmic patients described in the present study responded with the name "vanilla" 80 of 100 times, and another responded with the name "mint" 78 times.

To compensate for the possibility of a response bias, a ratio of the number of correct responses to the number of times chosen was calculated for each odorant. An analysis of variance for both percent correct and the above-noted ratio was calculated to determine if different odorants affected the percent correct on the OCM or the ratio differently. Because it is a routine part of the chemosensory evaluation, an assessment of gustatory ability was also performed.[12]

RESULTS

History. Six of the 22 patients related instances in which they had had difficulty in the early detection of the smoke from a fire. All these patients denied ever having had a sense of smell, and the concept of an odor was difficult for them to understand. None of these patients had a history that suggested that the olfactory deficit could have occurred as a result of an upper respiratory tract infection, nasal disease, toxic exposure, aging, or head trauma. Eight of the patients in the group reported a family history of a similar congenital olfactory problem in grandparents, parents, siblings, or offspring children (Fig 1).

A 27-year-old man in this group was diagnosed as having Kallmann's syndrome (hypogonadotropic hypogonadism) and a 24-year-old woman had reproductive and growth disturbances. None of the other patients had a history of endocrinologic problems; all had gone through puberty and showed signs of adult development (males with facial hair and/or male pattern baldness; females with regular menstruation and many with children).

Physical Examination, Imaging Studies, and Biopsies. The physical examination findings for the patients without associated anomalies were generally normal. The CT scans were reviewed for bony and mucosal abnormalities in the upper nasal and sinus cavities. Two of the 18 patients had unilateral choanal narrowing, 1 with a mild stenosis and 1 with an atresia. The olfactory clefts in these 2 patients appeared to be normal. Six patients had a minor degree of mucosal thickening in the paranasal sinuses, but the airways were patent. The CT scans of the remaining 10 patients were read as normal.

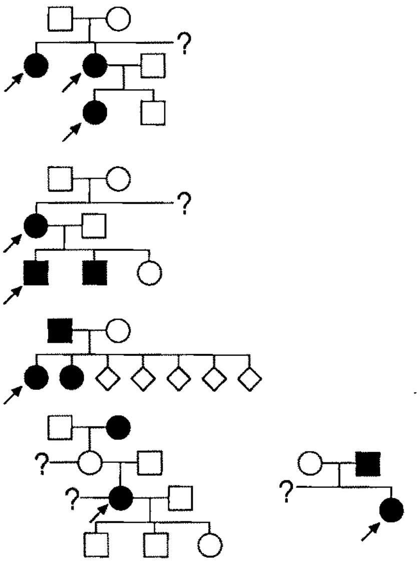

Fig 1. Pedigrees from patients who had congenital anosmia. Although only some of congenitally anosmic relatives received olfactory testing, all were said to have never had sense of smell. Dark symbols — congenitally anosmic individuals, squares — males, circles — females, diamonds — known offspring of unknown gender, question marks — unknown offspring, arrows — patients in present study.

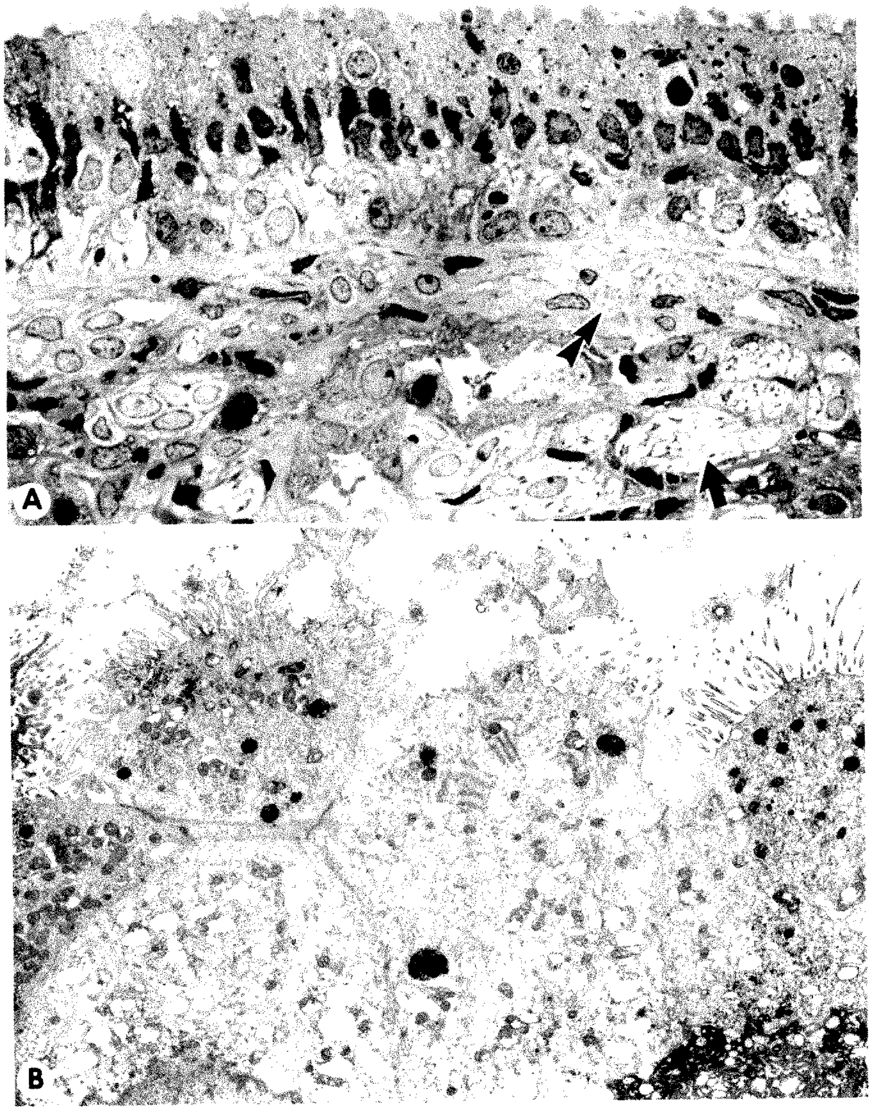

Fig 2. Olfactory mucosa, including both epithelium and lamina propria, harvested from 42-year-old woman with isolated congenital anosmia. A) Light micrograph illustrating presence of supporting cells and basal cells; there is no evidence of neurons in this particular field, although immature neurons were observed in other areas of biopsy specimen (original x720). Arrow — small fascicle of olfactory nerve containing swollen axons (comparable to area in Fig 3A), double arrowheads — swollen axons loose in lamina propria (comparable to area in Fig 3B). B) Electron micrograph of apical surface of epithelium showing typical microvillar-capped supporting cells and absence of olfactory knobs in this field (original x7,000).

The olfactory region of the nasal septum was submitted to biopsy in five patients (four sites in each patient). The results of these biopsies are best appreciated within the framework of the physiology and histology of the normal olfactory epithelium. It has been suggested that mammalian olfactory neurons have a life span of between 30 and 90 days.[13] At the beginning of its life cycle, a potential olfactory neuron will develop from an undifferentiated basal cell located deep in the olfactory epithelium. This emerging neuron will then send axons along the olfactory nerve toward the olfactory bulb. Once connections with the bulb have been made, the neuron will be able to function as a mature olfactory receptor. At the end of its life cycle, this cell will begin to degenerate and the connections with the olfactory bulb will be broken. The process of developing another olfactory receptor will then begin. If the neuron fails to make synaptic connections with the olfactory bulb, it will die before reaching the normal limit of its life span.[14]

Biopsies of the olfactory area usually show the presence of several different types of cells, including basal cells, supporting cells, and olfactory neurons at various stages of maturity. In the lamina propria, most of the axons seen are ensheathed by Schwann cells into fascicles, with each fascicle containing many axons. The mature axons are normally small, unmyelinated fibers that are fairly uniform in diameter.[15]

In three of the patients, no olfactory epithelium was found; instead, normal-appearing respiratory epithelium was identified. This result is consistent with the results of Jafek et al,[8] who recently found only respiratory epithelium in seven congenitally anosmic patients. In two of our patients — one the 27-year-old man with Kallmann's syndrome and the other a 42-year-old woman with isolated congenital anosmia — olfactory epithelium could be identified, but was highly abnormal in appearance. In both cases, the histopathology of the olfactory

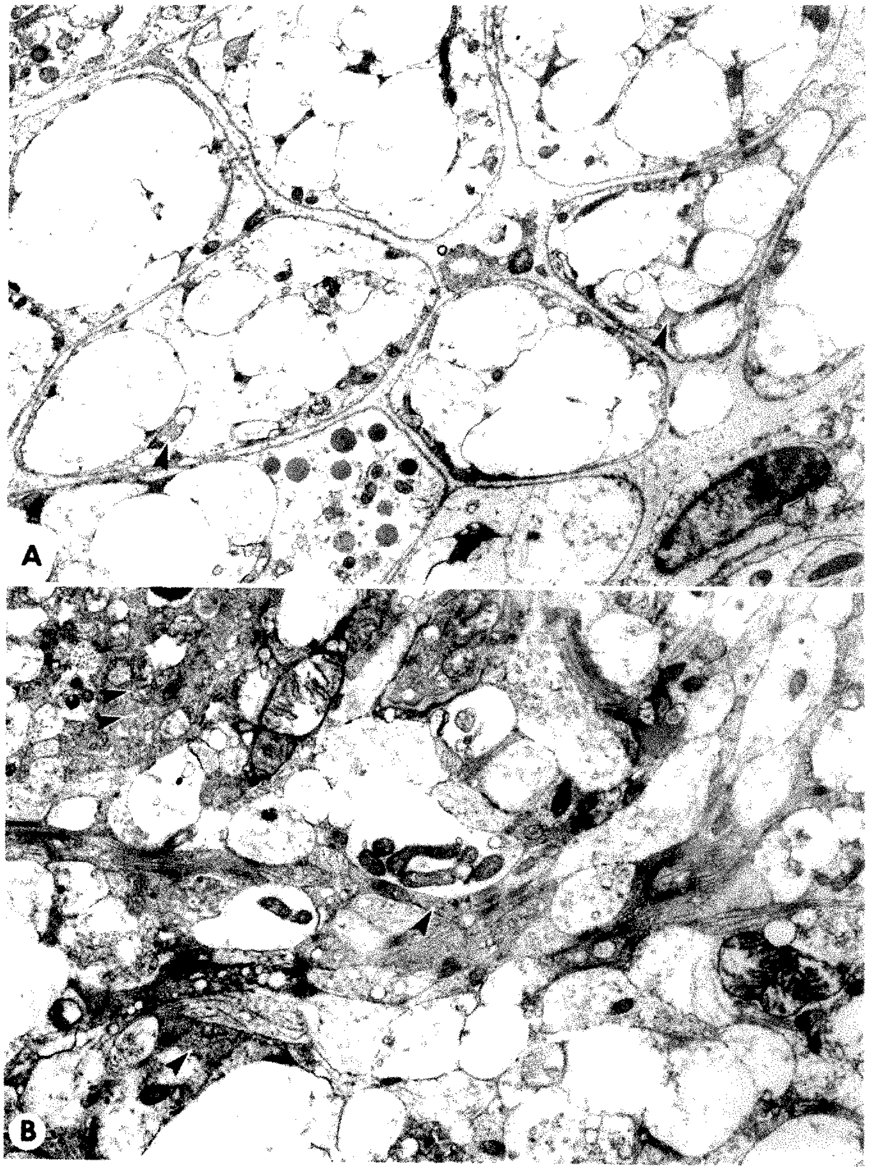

Fig 3. Same area of olfactory mucosa as shown in Fig 2. A) Electron micrograph illustrating fascicle of olfactory axons partitioned by tongues of Schwann cell cytoplasm (original x10,500). Vast majority of axons are swollen and their surface membranes are fragmented. However, some normal-appearing olfactory axons are seen (arrowheads). B) Electron micrograph of lamina propria illustrating disorganized knot of olfactory axons loose in connective tissue (original x15,500). Many axons are very swollen and fragmented, but some look normal (arrowheads) and others are intermediate in appearance.

epithelium was similar: supporting cells capped with microvilli and basal cells were present. Occasionally, immature olfactory neurons, identified by the absence of cilia on the olfactory knob, were also observed. However, there were no mature olfactory sensory neurons in these patches of epithelium (Fig 2). In the lamina propria deep to the epithelium, axons were abundant. They were found ensheathed by Schwann cells into fascicles, each fascicle containing many axons (Fig 3A). Other axons were found loose in the surrounding connective tissue or in dense neuromalike knots (Fig 3B). Most of these axons, irrespective of location, were swollen or broken open — an appearance that is indicative of axonal degeneration. Since some axons that were smaller and more normal in appearance were intermingled with the swollen atypical axons, it is unlikely that the observed axonal abnormalities are artifactual. On the basis of their abundance, their location throughout the lamina propria, and the nature of their ensheathment by Schwann cells, these axons are likely to be olfactory.

Chemosensory Testing. The overall percent correct of the 19 patients on whom olfactory testing was completed was 13%. (Chance performance for the OCM is 10%.) This score is also the lowest average percent correct of all the etiologic groups classified at the Olfactory Referral Center at Syracuse, eg, nasal disease, head trauma, upper respiratory tract infection, aging, etc.[16] An analysis of variance of the percent correct responses and the ratio of the number of times correct to the number of times chosen revealed no statistically significant difference across the 10 odorants. The mean percent correct and the mean ratio are shown by odorant in Table 2.

DISCUSSION

In the present study, 1 of the male patients had

TABLE 2. ANALYSIS OF OLFACTORY TEST RESULTS (AVERAGE OF ALL PATIENTS)

	% Correct	*No. Correct/ No. Times Chosen**
Ammonia	17.8	0.23
Cinnamon	11.0	0.12
Licorice	13.7	0.15
Mint	13.7	0.10
Mothballs	6.8	0.16
Orange	12.6	0.18
Rose	17.9	0.16
Rubbing alcohol	5.4	0.06
Vanilla	13.6	0.10
Vinegar	16.5	0.23

*To compensate for possibility of response bias.

Kallmann's syndrome, and 1 of the female patients had other endocrinologic defects. Additionally, 2 other patients had anatomic narrowing of the nasal choanae. Thus, of the 22 patients in the congenitally anosmic group, 18 (82%) were found to have none of the associated defects listed above. Likewise, Jafek et al[8] found that 6 of 7 (86%) of their patients had no defects associated with congenital anosmia. From both these studies it appears that congenital anosmia usually occurs without associated anomalies.

Recurring familial tendencies have been noted for congenital anosmia.[1,8,17-19] Lygonis[17] reported a dominant inheritance pattern that affected females approximately twice as often as males (19 females and 9 males in a family of 52 members over four generations). Likewise, Singh et al[1] reported a dominant inheritance pattern in an association of congenital anosmia, premature baldness, and vascular headaches. A review of the pedigrees of the patients included in the present study showed similarities to the inheritance patterns observed by both Lygonis and Singh et al. The inheritance patterns in the present study were autosomal, and because of difficulties in the identification and reporting of congenital anosmia in other family members, likely dominant. Moreover, we observed a female predominance of approximately 2 to 1.

Little is known of the pathophysiologic basis for congenital anosmia with or without associated anomalies. In Kallmann's syndrome, the olfactory bulbs are reportedly absent.[20] Similarly, midline facial defects can be associated with congenital anosmia and absence of the olfactory bulbs.[10] The presence of olfactory epithelium in our patient with Kallmann's syndrome is an indication, therefore, that absence of the olfactory bulbs is not necessarily associated with the failure of formation of the olfactory epithelium. Indeed, our observations of immature olfactory neurons in association with dilated, degenerating olfactory axons indicate that olfactory neurons are present in the mucosal lining and still send out axons in an attempt to contact the bulb. These degenerative changes in the olfactory axons are reminiscent of alterations observed in anosmia following head trauma[21] (also J. E. Schwob, unpublished observations, 1990) and in experimental animals following removal of the olfactory bulbs.[14]

Olfactory epithelium was also identified by biopsy in one of our patients who was judged to have congenital anosmia without associated anomalies. Similarly, Douek et al[22] reported that olfactory epithelium was harvested from a patient with isolated congenital anosmia. In both cases, axonal abnormalities and the absence of mature olfactory neurons were observed. Considering the histopathologic findings in these cases, we think that perhaps in at least some patients with congenital anosmia, the olfactory deficit may be due to a failure of the olfactory neurons to contact an existing olfactory bulb. As another possibility, the olfactory bulbs in these patients may be absent, representing an isolated developmental abnormality. In either case, the abnormalities observed in the olfactory epithelium would reflect the inability of olfactory neurons to contact the bulb and the enhanced neuronal turnover that would occur as a consequence.[14]

Klingmuller et al[23] recently developed magnetic resonance techniques to image the olfactory sulcus. It will be interesting to use these techniques to determine which congenitally anosmic patients lack normal olfactory sulci.

Thirteen percent was the mean overall percent correct of the 19 congenitally anosmic patients on whom olfactory testing was completed. The 95% confidence interval for this mean is 10 to 16, suggesting that 13% is not significantly different from the 10% chance level. This observation is consistent with the results of both Jafek et al[8] and Davidson et al,[24] who report that congenitally anosmic patients test only slightly above the chance level on other standard olfactory tests.

An analysis of variance of the percent correct and the ratio of the number of times correct to the number of times an item was chosen revealed no statistically significant difference across the 10 odorants ($p > .05$). Given the nature of the odorants in the OCM, this result is somewhat surprising. The 10 odorants of the OCM include some odorants that stimulate mostly the trigeminal nerve (ammonia and vinegar) and others that stimulate mostly the olfactory nerve (rose and vanilla). The other 6 odors in the test are mixed stimulators, affecting both the trigeminal and olfactory nerves. Since no statistically significant difference was found in the identifiability of the 10 odorants on the OCM, the results of the present study suggest that congenitally anosmic patients can detect neither olfactory nor trigeminal chemosensory signals.

However, some caution must be exercised in suggesting this conclusion. It should be recalled that the OCM is an identification test. It is possible that at least some of the chemosensory signals are being detected, but the patients cannot make the proper identification. That is, patients might know that something is there but not be able to give the stimulus the correct name.

Although not statistically significant, an analysis by odorant of the ratio of the number correct to the number of times an odorant was chosen suggests the possibility of at least some trigeminal function in many of the patients. As can be seen in Table 1, ammonia and vinegar (the two strongest trigeminal stimulators) had the highest ratio. In other words, when subjects indicated either ammonia or vinegar, they were more likely to be correct. It may be that these patients felt "something" from the stimulation of the trigeminal nerve, and so limited their responses to either ammonia or vinegar. This narrowing of choices might then have resulted in a greater likelihood of correct identification of the odorants.

However, for several of the patients in this study there is no evidence of either trigeminal or olfactory function. Perhaps, as Jafek et al[8] suggest, the problem with some congenital anosmics may be central. Thus, no airborne stimuli are likely to be detected.

Results of tests of gustatory function in the present study were all normal — an observation that is consistent with the experience of Jafek et al.[8] The presence of functional taste buds should be pointed out to the patient as a positive factor for improving his or her eating experience.

Imaging studies using CT scanning were useful in separating patients who had obstructive nasal inflammatory disease from those with congenital olfactory deficits. As noted above, several of the patients with congenital deficits did have some thickening of the membranes of the nasal cavity and sinuses. However, in all cases, the passageway to the olfactory receptors in the olfactory cleft was patent.

As Jafek et al[8] suggest, another aid to the diagnosis of congenital anosmia is a trial of oral steroid medication. If the olfactory ability improves with this challenge, then the patient cannot be classified as having congenital anosmia.

Once the diagnosis of a congenital lack of olfactory ability is made, decisions regarding management are unfortunately limited. For virtually every congenital anosmic, there is no known method for restoring olfactory ability. For this reason, these patients should be counseled so that they do not waste effort and expense trying to establish a sense of smell. In addition, caution must be observed regarding fires and dangerous fumes, and multiple smoke and explosive gas detectors in the home are a worthwhile investment.

Fortunately, congenitally anosmic patients generally do not consume sweet and salty foods in an unhealthy manner — an eating pattern that is sometimes seen in patients who have lost a previously intact sense of smell. It should also be noted that in general, patients in the congenital group are not unhappy, since they never experienced a sense of smell and therefore do not realize what they are missing.

CONCLUSION

A detailed history, physical examination, chemosensory evaluation, olfactory biopsies, and imaging studies were conducted on patients with a congenital lack of olfactory ability. These patients reported never having smelled anything, and the concept of odor was difficult for them to understand. Although the physical examination findings were generally normal, in a few patients the anosmia was accompanied by other anomalies, including endocrine and nasal anatomic abnormalities. Results from the OCM suggest a generalized inability to detect airborne odorants, including both trigeminal and olfactory nerve stimulators. However, in many patients there was at least a suggestion of some trigeminal function. Biopsy showed the presence of olfactory epithelium in some of the patients, but it was abnormal in appearance.

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ROLE OF INJECTABLE COLLAGEN IN THE TREATMENT OF GLOTTIC INSUFFICIENCY: A STUDY OF 119 PATIENTS

CHARLES N. FORD, MD
DIANE M. BLESS, PHD
JEAN M. LOFTUS, MD
MADISON, WISCONSIN

Injectable bovine collagen has been used for treatment of glottic insufficiency at the University of Wisconsin Clinical Science Center since 1983. This report reviews our experience in treating 119 patients with a variety of vocal fold disorders manifested by glottic insufficiency. Many of the patients were referred because of prior treatment failures or problems that were impossible to treat with other modalities. Results were assessed by comprehensive voice evaluations using subjective patient self-assessments, perceptual judgments made by a panel of experts who had no prior knowledge of the study, objective assessments, and videostroboscopy. Objective assessment included vocal function measures and acoustic analysis. Results indicate that collagen not only is comparable to other injection filler substances but also has unique advantages as a bioimplant. Collagen injection seems uniquely suited for treatment of several problems, including vocal fold atrophy, focal defects, minimal glottic insufficiency, and scarred vocal folds that are not managed optimally with Teflon injection. Overall there were no serious complications and treatment was effective for a broad spectrum of problems. In most instances the correction persisted, and in those instances in which injected collagen seemed improperly distributed, the vocal fold was recontoured or the implant removed without appreciable damage to the surrounding tissues. Injectable collagen has been extensively studied and deserves to be included in the armamentarium of the laryngeal surgeon.

KEY WORDS — collagen, larynx, vocal fold, voice.

INTRODUCTION

The search for an ideal substance for vocal fold augmentation led Arnold[1] to use Teflon (Polytef Paste), which has become the workhorse method for treating glottic insufficiency. Although Teflon injection has offered tremendous improvement, this alloplastic preparation induces a definite foreign body reaction and focal fibrosis.[2-5] Concerns about complications such as granuloma formation,[6,7] airway obstruction,[8,9] potentially irreversible damage to vocal fold vibratory structure by foreign body reaction and fibrosis,[10] and the possibility of implant extrusion or migration[11,12] have motivated clinicians to look for alternative forms of treatment. Such alternatives have been advocated to enhance voice results and provide greater flexibility without permanently altering vocal fold tissues.[13-15]

Collagen injection differs from other vocal fold medialization approaches in that it is a biological implant, providing more than medial displacement of the vocal fold. The collagen implant consists of bovine collagen modified by solubilization and cross-linking to reduce cellular and humoral host immune response, but it is histologically similar to the deep lamina propria tissues in the vocal fold. Host tolerance of injected collagen is characterized by gradual assimilation starting with ingrowth of vessels and progressive invasion of fibroblasts into the implanted collagen. The events following collagen injection that affect vocal fold function specifically include the gradual variable resorption of injected collagen, the replacement of some resorbed implant by deposition of new host collagen from metabolically active invading host fibroblasts, and the softening of existing scar tissue, probably due to fibroblastic production of collagenase.

The physiologic limitations of alloplastic augmentation and the theoretic advantages of bioimplantable materials have led to experimentation with collagen injection of the vocal fold. Injected soluble bovine collagen has been used successfully to augment dermal defects and to soften depressed scars. We reasoned that this collagen implant might be well tolerated in the collagen-containing layers of the vocal fold and might be useful in treating scarred larynges.

PREVIOUS WORK

These observations prompted us to compare collagen injection to Teflon injection in dog larynges[16] and to look at the long-term histologic fate of different forms of collagen injected into the canine vocal fold.[17] We found that collagen could be injected precisely through a 26-gauge needle into the deep lamina propria of the vocal fold — a site normally composed of dense collagen. The implant was remarkably well tolerated, with no evidence of foreign body or inflammatory reaction; over time there was some peripheral neovascularization and ingrowth of fibroblasts with deposition of scattered

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From the Division of Otolaryngology, Department of Surgery (all authors), and the Department of Communicative Disorders (Bless), University of Wisconsin, Madison, Wisconsin. This work was supported in part by grants from the Food and Drug Administration, Orphaned Product Development Division (grant FD-R-000404-02), the Veterans Administration Rehabilitation Research and Development Service, and a General Research Support Grant to the University of Wisconsin Medical School from the National Institutes of Health Division of Research Facilities and Resources (project 133-H529).

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foci of new host collagen within the implant matrix, replacing some of the assimilated implant. Persistence of the implant was noted at intervals up to 1 year. Similar results were obtained subsequently by Okamoto.[18]

We also looked at the effect of superficially injected collagen on vocal fold vibration in the excised larynx and noted that simulated deficiencies could be corrected, with correction resulting in normal passive activation of vibratory activity in response to a steady controlled subglottic air pressure.[19] Recent in vivo canine studies have demonstrated improvement in many vocal function parameters following injection for simulated vocal fold paralysis.[20]

In 1985 the authors[21] presented the first clinical trials of Zyderm Collagen Implant (Collagen Corp, Palo Alto, Calif) to correct glottic insufficiency in 27 patients. Objective voice analysis demonstrated efficacy, and none of these patients suffered complications. Questions were raised regarding long-term persistence of the implant and the possibility of hypersensitivity reactions.[22] A subsequent report with 2-year follow-up data indicated that in most patients, correction evident at 1 to 3 months persisted and results stabilized.[23] In this group of 44 patients, there was 1 with a delayed hypersensitivity reaction manifested by development of slight redness at the vocal fold and skin test site at 5 weeks. Since 1986 all patients have been injected with cross-linked collagen preparations (generic glutaraldehyde cross-linked [GAX] collagen, also marketed as Zyplast and Phonagel), which are less antigenic, diffuse easily, and undergo less initial shrinkage after injection.

Failure to gain Food and Drug Administration (FDA) approval limited clinical trials in this country, but others[24-29] have reported successful results with soluble collagen injections for glottic insufficiency. Most of these investigators made the injections in the superficial mucosal layers of the vocal fold, since it was demonstrated that collagen injected deep in vocalis muscle was rapidly resorbed.[17] The issue of resorption was addressed in two postmortem studies. Remacle and Marbaix[30] reported on the persistence of injected collagen in postmortem human larynges up to 5 months postinjection, and Ford et al[31] noted persistence in one patient after 1 year.

It was apparent from these initial studies that collagen injection was a successful treatment for a variety of pathologic disorders manifested by glottic insufficiency. The limitations of Teflon injection did not seem to apply to collagen, especially in the treatment of the scarred vocal fold, focal defects, atrophy, and limited glottic insufficiency problems. Efficacy was demonstrated in independent studies of patients with age-related changes in the vocal folds (presbylaryngis)[32] and in those with scarred larynges.[33]

PURPOSE OF STUDY

In an attempt to further explore the potentials of a biologic implant, we initiated a study (suppported by the Orphaned Products Division of the FDA) to treat glottic insufficiency in patients who were not optimal candidates for Teflon injection, and we reviewed the entire group of collagen-injected patients treated at the University of Wisconsin Clinical Science Center. Demonstration of efficacy in that select group of patients seemed a sufficiently important endeavor that no attempt was made to compare efficacy of collagen with other modes of treatment.

MATERIALS AND METHODS

Collagen injection of the vocal fold has been performed at the University of Wisconsin for management of glottic insufficiency since 1983. Goals included improving glottic closure, vocal quality, ease of phonation, and associated laryngeal functions in patients with a variety of vocal fold disorders. The experimental protocol was initiated in 166 patients, of whom 26 were lost to follow-up, 5 were treated too recently to include, and 2 had nonvoice problems. Fourteen patients were not treated: 4 had positive skin tests, 4 declined in favor of alternative forms of treatment, 3 had marginal airways, and 3 improved with voice therapy.

PATIENTS

The 119 patients reported in this study represent those individuals who were treated and who complied with our protocol for follow-up voice assessment data collection. The pretreatment age range was 17 to 87 years, with a mean of 56 years, and the male to female ratio was approximately 3:2. Nearly half of the patients treated had scarred larynges, often secondary to laryngeal cancer surgery — a fact reflected in the male preponderance, for laryngeal cancer remains a predominantly male disease. Patients had experienced voice problems for an average of 6.1 (0.08 to 33.9) years before treatment and 30% had undergone voice therapy prior to collagen injection. Some patients underwent more than one injection over a period of months or years. The average length of follow-up was 16.4 (1 to 67) months.

Potential patients were evaluated by a speech pathologist and the senior author (C.N.F.) to determine their suitability for treatment. In each case both the protocol and available alternatives to management were described. Those who seriously considered collagen injection were skin-tested with Zyderm, which is generically similar to GAX collagen but exhibits greater antigenicity. If the skin test remained negative for 6 weeks, injection was offered. Two patients were injected before 6 weeks because of severe aspiration problems.

Each patient was assigned to one of three vocal fold disorder groups on the basis of those histopathologic findings that seem to affect function and outcome.

Scarred Vocal Fold. The scarred vocal fold group were patients who had evidence of vocal fold scarring manifested by stiffness or decreased mucosal wave on videostroboscopy. Such patients typically had the most impaired vocal fold vibration, often secondary to surgery such as cordectomy, vocal fold stripping, Teflon injection/or removal, and hemilaryngectomy. Other patients had undergone radiotherapy or prolonged endotracheal intubation.

Bilateral Disorder. The bilateral vocal fold disorder group comprised patients who had had some form of bilateral disorder without scar formation. These patients exhibited a variety of diagnoses, including neurologic disorders such as presbylaryngis, Parkinson's disease, and abductor spasmodic dysphonia with bowed vocal folds. Some of these patients showed atrophic changes associated with presbylaryngis as well as bilateral paresis. Bilateral paresis was also attributable to head injuries, respiratory infections, and idiopathic neuropathies.

Unilateral Disorder. The unilateral vocal fold disorder group was made up of patients who had essentially unilateral disorders without evidence of scar formation or contralateral vocal fold disorders. Some had iatrogenic injuries involving the recurrent and/or superior laryngeal nerves. Other patients were paretic or paralyzed as a result of cerebral vascular accident or prolonged intubation, and some cases were idiopathic.

Patients with mixed disorders were assigned to that group typically associated with their greatest impairment of vocal fold function according to the following hierarchy: scarred vocal fold > bilateral disorder > unilateral disorder. The FDA Orphaned Product study was limited to the most severely impaired larynges; these patients had mainly scarred vocal folds or bilateral disorders.

COLLAGEN

The material injected during the initial phase of this study consisted of Zyderm Collagen Implant, a soluble bovine collagen. Since 1986 we have used GAX collagen, an injectable glutaraldehyde cross-linked (0.0075%) fibrillar collagen (Zyplast, Phonagel). It is essentially type I collagen with a residue of 1% to 5% type III collagen, prepared by selective hydrolysis of the nonhelical amino-terminal and carboxy-terminal segments (telopeptides) of the collagen molecule. Antigenicity is reduced by telopeptide cleavage and further reduced during the cross-linking process. GAX collagen remains the preferred material for vocal fold injection because it persists with minimal shrinkage and has reduced antigenicity compared to other forms of injectable collagen.[34]

PROCEDURE

Most of the injections were made by using indirect laryngoscopy and topical anesthesia, but several patients, particularly in the scarred vocal fold group, required direct microlaryngoscopy for proper placement. The material was injected via a device designed by the senior author[35] through the superior surface of the vocal fold into the intermediate and deep lamina propria.[21,23] The 26-gauge needle allowed for precise visual and tactile placement at the plane of the vocal ligament; slight resistance is encountered as the needle is advanced from the superior surface further into the vocal fold tissue.[36] In heavily scarred larynges, an effort was made to get as much collagen injected into the scar as possible with the initial penetration; often this practice resulted in collagen's being dispersed in deeper or more superficial levels than would have been ideal. Subsequent injections were generally easier and more precisely placed. All injections were made on a distinctly more superficial plane than is typical with Teflon, silicone, Gelfoam, or fat. The superficial placement facilitates filling in focal defects without distorting the entire vocal fold, prevents rapid resorption, and allows the implant to be injected at a site in which collagen is normally found.

In some of the more complex cases, collagen injection was used to enhance or correct changes induced by other forms of therapy. For example, patients with fibrotic convex vocal folds secondary to Teflon granulomas were managed by endoscopic removal of Teflon; in those instances in which the medial edge remained irregular, the vocal fold was remodeled with precise injections of collagen. Four patients had sulcus vocalis deformities treated by cordotomy, lysis of the adhesions, and later collagen injection to contour and soften the vocal fold tissues. Several patients were referred because failed attempts at glottic reconstruction following various conservation laryngectomy procedures left them with stiff, scarred larynges incapable of useful phonation. One patient had bilateral vocal fold paralysis and a marginal airway unsafe for any vocal fold augmentation; after successful neuromuscular pedicle transfer to the posterior cricoarytenoid muscle, a small amount of collagen was injected unilaterally in the membranous vocal fold with perceptible improvement in voice and no change in exercise tolerance. Some patients with scarred larynges had large glottic gaps that were initially addressed with thyroplasty surgery, and the scarred vocal fold was treated with collagen injection to soften and restore the contour of the vocal fold.

Postoperatively, patients were observed for airway problems and kept on relative voice rest overnight — talking only when necessary and avoiding extremes in pitch and loudness. Patients returned for full assessment at 1-, 3-, and 6-month and 1-year intervals. Subsequent data were collected on a yearly basis.

ASSESSMENT METHODS

Four general categories of voice assessment were used to measure treatment success: 1) subjective patient self-assessment of voice quality and effort of phonation, 2) perceptual judgments of voice recordings by an impartial panel of experts, 3) laboratory data based on acoustic signal analysis and aerodynamic measures during voice production, and 4) studies of the appearance of vocal fold vibration by videostroboscopy.

Subjective patient self-assessment ratings were included as part of this comprehensive voice evaluation. After treatment, patients were grouped on the basis of their own ratings of their vocal quality and the effort required to produce phonation: 1) voice not improved, 2) voice improved and sustained improvement, 3) transient improvement, and 4) voice worse. Some patients in group 2 (bilateral disorders) noted a very slight decrement in vocal function over time but were convinced that the voice was substantially improved over the pretreatment status. For patients who had multiple injections, the subjective category was based on comparing the most recent evaluation to that immediately before the last injection.

Audiotape recordings were made in a sound-controlled booth with a Nagra tape recorder, as previously described.[21] The test sample recorded included sustained vowels /a/ and /i/ produced at normal pitch and loudness and the sentence "The blue spot is on the key" produced at conversational level. These samples were used for both the acoustic and perceptual analyses.

Perceptual judgments were made from the audio recordings of sustained vowels and the standard sentence. Pretreatment and the most recent posttreatment recordings were randomized and paired on a master tape. Three experienced speech pathologists were asked to make paired comparison judgments to determine which sample, if either, sounded better; they also indicated when there was no appreciable difference. To determine reliability of judgments, 10% of the samples were repeated and 10% of the samples were foils consisting of two identical samples. Foils were used to determine validity of the perceptual ratings. The judges were 100% correct in judging these voices to be the same.

Acoustic analysis of voice production permits quantitative analysis of the multidimensional physical characteristics of the voice signal and inference about the underlying physiologic mechanism. Samples were digitized on an IBM-PC computer with a locally developed software program (C-Speech). Jitter, shimmer, and signal to noise ratio (SNR) were derived by using the least mean square fit of a waveform model to the speech waveform.

TABLE 1. SUBJECTIVE PATIENT SELF-ASSESSMENT REGARDING VOICE QUALITY AND EFFORT

Disorder	*N*	*Sustained Improvement*	*Transient Improvement*	*No Improvement*	*Worse*
Scarred vocal fold	55	39	4	12	0
Bilateral disorder	25	23	1	1	0
Unilateral disorder	39	39	0	0	0

Data are numbers of patients.

Vocal function measures were recorded by means of a face mask attached to the Nagashima PS-77 Phonatory Function Analyzer to obtain maximal intensity (decibels) and mean airflow (milliters per second). Transglottic airflow was assessed during production of /a/ and /i/ during a variety of phonatory tasks. High airflows were considered an indicator of poor laryngeal closure, as might occur in glottic insufficiency. Low airflows generally signified a competent glottis, but were noted to occur also with hyperfunction of laryngeal structures (a common compensatory activity), obstruction, low patient effort, or poor respiratory support.

Vocal fold vibration was observed with a Bruel & Kjaer laryngeal videostroboscope coupled to a rigid 90°-angled Wolfe endoscope and videorecorder. Recordings were used to assess ongoing treatment and to study individual cases over time. Recordings were rated in 15 consecutive cases by trained observers who made qualitative judgments of vocal fold vibration and supraventricular hyperfunction. Parameters observed were symmetry, periodicity, glottic closure, vibration amplitude, mucosal wave, and supraventricular hyperfunction; preoperative and postoperative samples were compared for each patient.

In cases for which preinjection data were available from more than one date, the date closest to injection was selected. Postinjection data were selected from the latest date the patient had been evaluated. When collagen injection was done after thyroplasty, Teflon removal, or reinnervation surgery, baseline measures were taken after the previous operation and before collagen injection.

STATISTICAL ANALYSIS

Efficacy of collagen injections was addressed by asking two questions: 1) Was there a significant change in any of the variables postinjection? and 2) Was there any difference between disorder groups in response to the collagen treatment? To analyze for pretreatment and posttreatment changes in the parameters (acoustic, aerodynamic, perceptual), we used paired *t* tests to determine whether or not

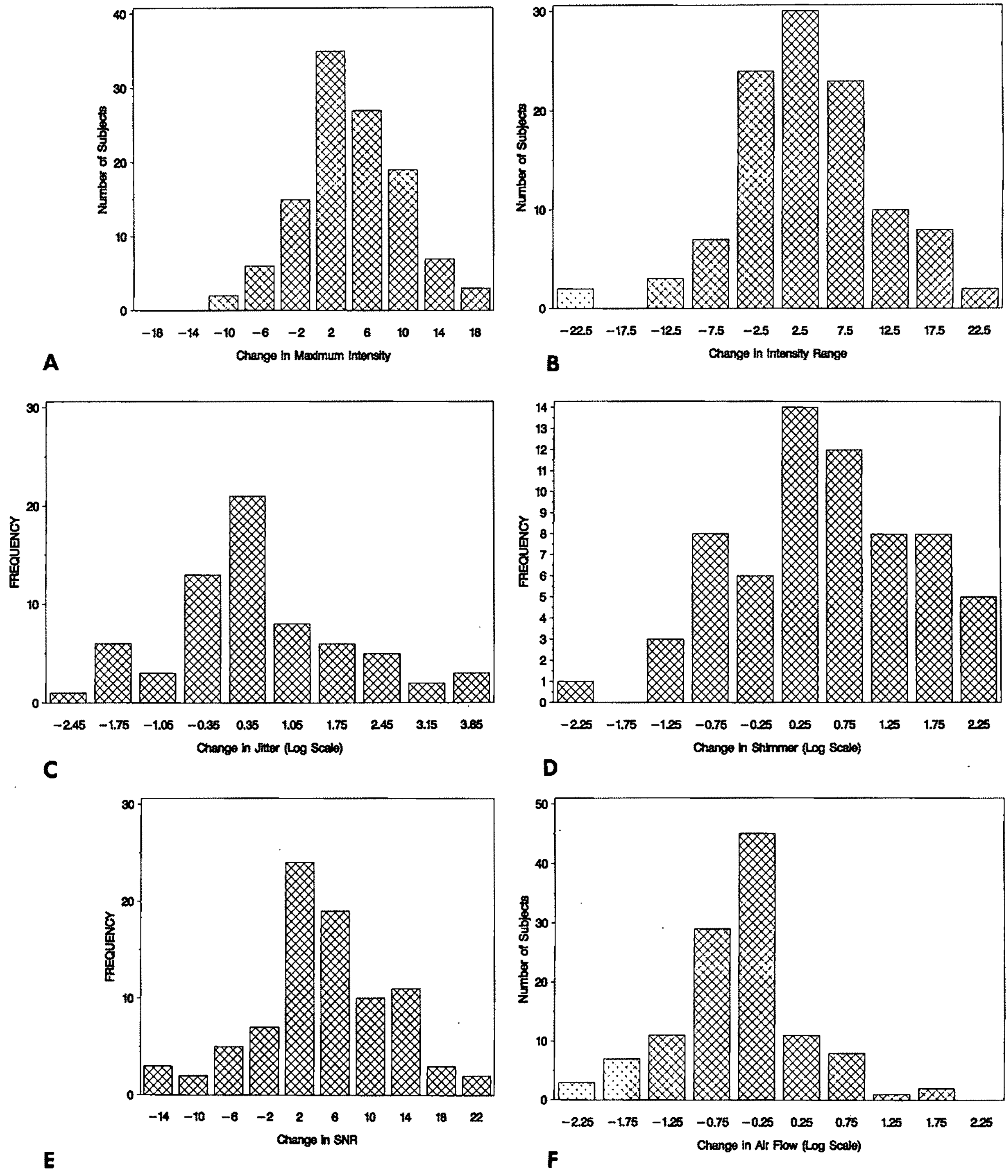

Fig 1. Bar graphs of changes from before to after collagen injection for six measures of vocal function. A) Maximum intensity. B) Intensity range. C) Jitter. D) Shimmer. E) Signal to noise ratio (SNR). F) Airflow.

the mean change was equal to zero. Differences between diagnosis groups were studied by using an analysis of variance. A χ^2 test was used for overall testing of perceptual change within and between groups. For measures with skewed distributions (airflow, jitter, shimmer), the log of the measure was used. These transformed measures had distributions close to normal, thus making the transformation changes nearly equivalent to analyzing percentage changes rather than absolute changes. Pearson's product-moment correlations were used to assess intrajudge and interjudge reliability. Wilcoxon's test was used to test for differences between stroboscopic recordings for select patients. The test

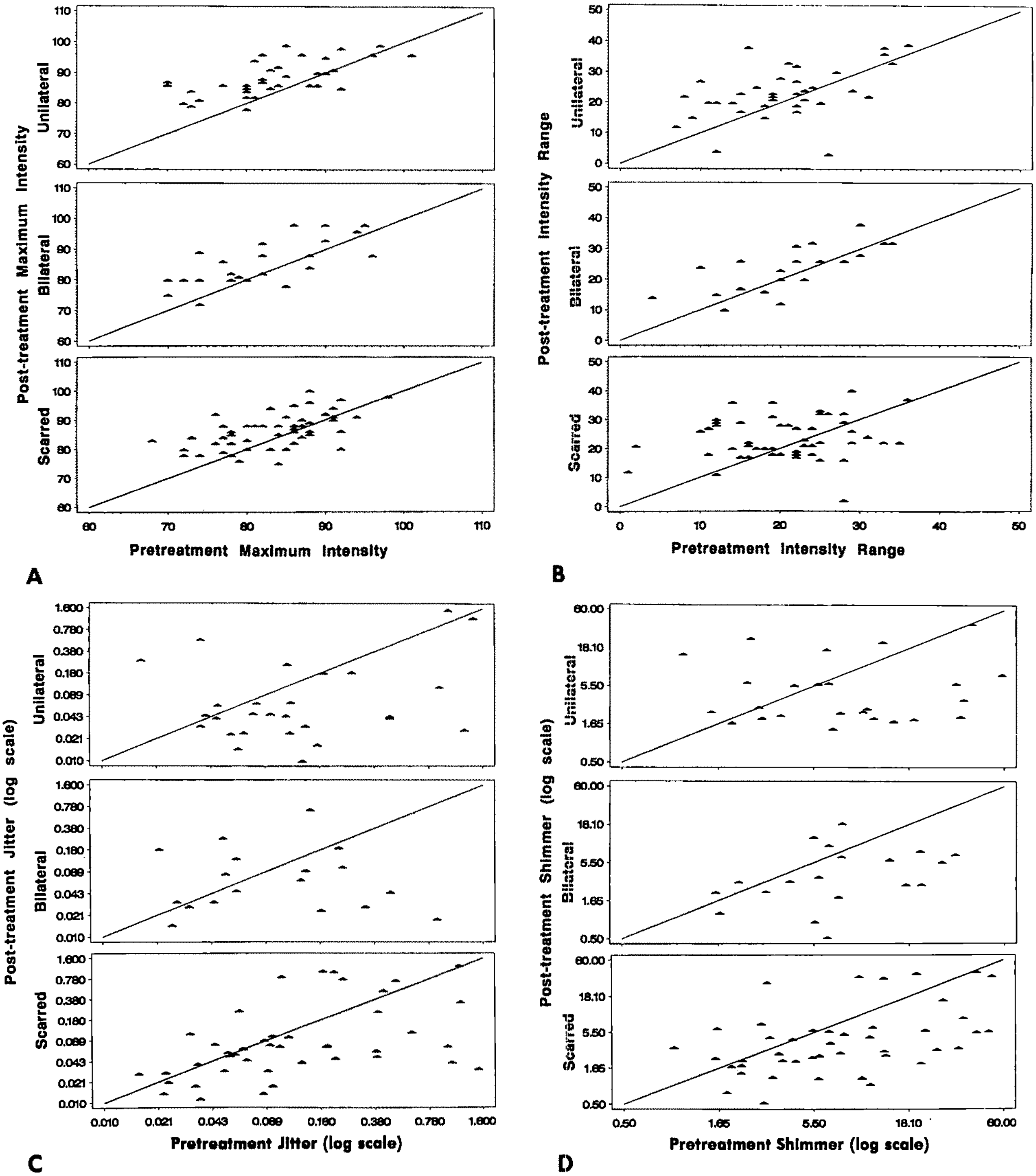

Fig 2. Scatterplots of three treatment groups' performance on measures of vocal function before and after collagen injections. A) Maximum intensity. B) Intensity range. C) Jitter. D) Shimmer. (Continued on next page.)

assumes that the distribution of the data is symmetric about the median.

RESULTS

There were no serious complications or side effects for any of the 119 patients. Two reactions to Zyderm injection in the vocal fold could be considered delayed hypersensitivity reactions. In 1 patient redness was noted at the injection site and developed at the skin test site 5 weeks after the initial skin test and 1 week after vocal fold injection. The second patient developed redness of the injected vocal fold at 1 year postinjection. Neither of these patients experienced any airway compromise and both noted improved voice that persisted. Interestingly, they were both alcoholics, heavy smok-

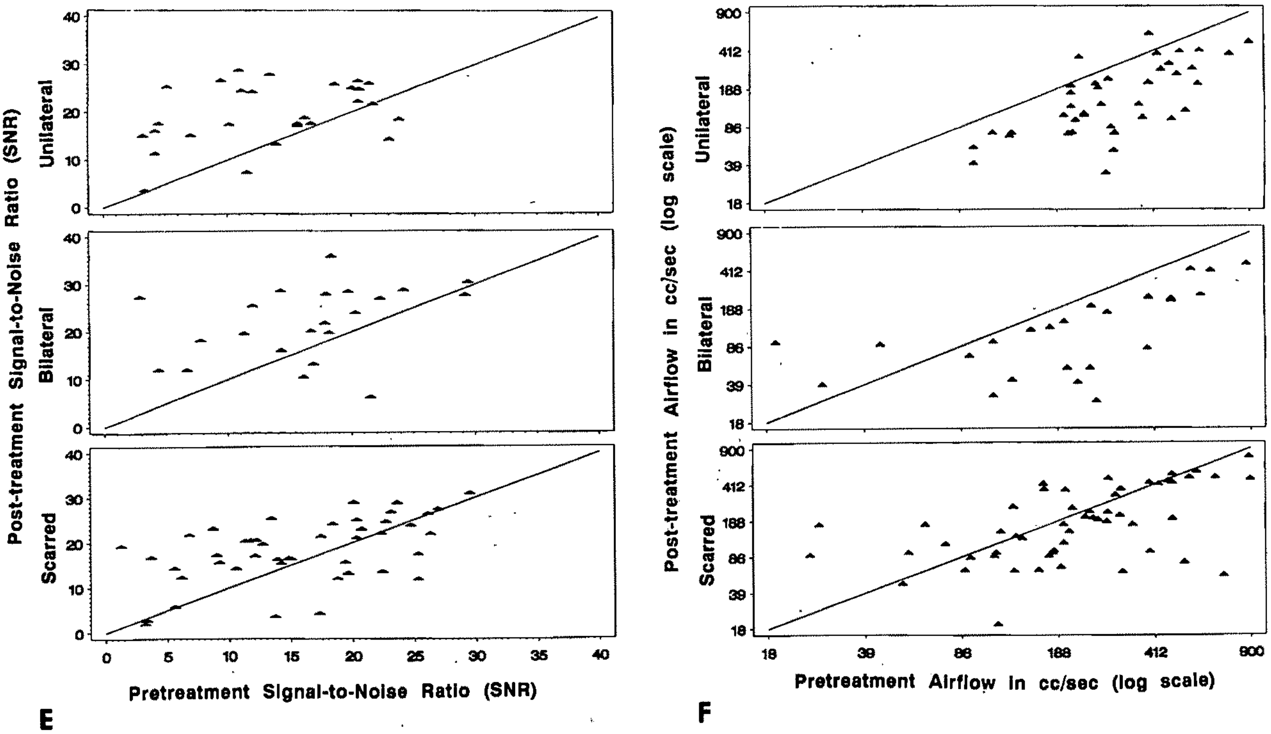

Fig 2, continued. E) Signal to noise ratio. F) Airflow.

ers, and posthemilaryngectomy men who had been injected with Zyderm in 1984. There have been no apparent hypersensitivity reactions to GAX collagen injections.

In the subjective patient assessment (Table 1), those in the unilateral paralysis group all rated their voices improved, and improvement over preinjection status was noted throughout the follow-up period. Those with scarred larynges had the worst ratings, with 12 patients noting no appreciable improvement. No patient felt the voice was worse following collagen injection. In 3 patients with scarred larynges, the surgeon noted qualitative changes such as diplophonia and inappropriately elevated pitch that appeared to be related to focal loculations of implanted collagen at superficial sites. In each of those patients a small incision was made over the implant bleb and the material easily aspirated; this procedure resulted in improved contour and subjective vocal quality. Improvement was noted by perceptual judgments, and the significance varied by diagnostic group. In comparing pretreatment to posttreatment assessments the overall improvement was significant at $p = .00023$ (unilateral $p = .021$, bilateral $p = .71$, and scarred $p = = .0009$).

Acoustic measures evaluated from pretreatment to posttreatment included maximum intensity, intensity range, jitter, shimmer, airflow, and SNR (Figs 1 and 2). In general, maximum intensity, intensity range, shimmer, and SNR increased and jitter and airflow decreased. Results were predicted (Table 2) as a function of the anatomic changes achieved through the collagen injections.

Successful injection for glottic insufficiency should result in improved glottic closure such that there is less wasted airflow during phonation. Although some patients have a tendency to compensate for glottic insufficiency by supraglottic valving, which also decreases flow, reduced airflow following injection was generally considered to indicate success. Low preoperative flows (<80 mL/s) increased (Fig 2F), and high flows (>200 mL/s) decreased, regardless of the disorder classification.

Significant differences were determined for all groups for six objective parameters (Table 3). One of the greatest changes for the unilateral group was airflow. Both the bilateral and scarred groups also showed significant airflow changes, but the significance in the scarred group was marginal. Maximum

TABLE 2. SELECTED VOCAL PARAMETERS AND HOW THEY SHOULD CHANGE AS FUNCTION OF TREATMENT GOALS

Treatment Goal	*Intensity*	*Airflow*	*Frequency*	*Jitter*	*Shimmer*	*SNR*
Improved closure	+	–	–	–	–	+
Decreased stiffness	+	–	–	+	0	+
Improved vocal fold contour	+	–	0	–	0	+
Reduced hyperfunction	0	+	0	+	0	0

SNR — signal to noise ratio, plus — should increase, minus — should decrease, zero — no predictable change.

TABLE 3. SIGNIFICANT DIFFERENCES FOR THREE DISORDER GROUPS ON SIX OBJECTIVE VOCAL PARAMETERS

	Disorder Groups		
Vocal Parameters	*Scarred*	*Bilateral*	*Unilateral*
Airflow	+	++	++
Maximum intensity	++	++	++
Signal to noise ratio	++	++	++
Intensity range	++	–	+
Jitter	++	–	++
Shimmer	++	++	++

Two pluses — significantly different, one plus — significantly different but marginally so, minus — not significantly different.

intensity and SNR increased significantly for all three groups. For the scarred group, intensity range, jitter, and shimmer also increased significantly. Both jitter and shimmer were significantly increased for the unilateral disorder group.

Videostroboscopy was particularly helpful in assessing individual patients and in guiding initial placement and modification. It was difficult to objectively assess results of collagen injections by using videostroboscopy, because the medialized vocal fold was usually obvious in the postoperative sample. Recognition of the postinjection samples did not interfere with ratings of supraglottic hyperfunction, waveform periodicity, glottic gap, amplitude of vibration, mucosal wave, and vocal fold symmetry. These measures were rated on preoperative and postoperative videotapes and the results subjected to statistical analysis with Wilcoxon's test (Table 4). These data suggest a significant improvement in all videostroboscopic parameters.

DISCUSSION

SUBJECTIVE MEASURES

In this study, voice improvement was determined by both subjective and objective measures. Patient self-assessments were, overall, higher than the perceptual judgments of the panel of experts; the professional did not note improvement unless the voice was less hoarse, whereas the patient self-assessment included not only quality, but also effort and loudness.

In many patients the primary concern was the extreme effort and dyspnea of phonation; another frequent concern was inadequate vocal volume. After successful treatment, patients perceived a louder voice as improved because they could carry on a more normal life talking over noise in restaurants, cars, etc. Improved closure would often result in increased intensity levels even when quality was not changed. Although such changes may not have been apparent to the listener, for the speaker they were very important.

The patient self-assessments related well to the measures of airflow, SNR, and intensity. One might be tempted to explain the difference between the patient self-assessment and professional perceptual ratings on the probability that the patient expects changes to result from therapy, and therefore rates his or her voice as improved. The correlation of self-assessment ratings with objective measures and analysis of ratings in different disorder groups suggest more fundamental differences. The scarred group had the worst voice both preoperatively and postoperatively, but the panel of speech pathologists noted more individuals with improved voice in this group than in the other two. Some of these patients started out aphonic or nearly aphonic with very high harmonics. Thus, any treatment resulting in some voice or reduction in the higher harmonics would be rated by the speech pathologist as improved. The bilateral group generally began with some voice, though often characterized by weakness, breathiness, and poor control. This group also had the most individuals with other neurologic and respiratory problems that were often not treated and that continued to contribute to the overall quality of voice. Following treatment, the voice was louder and therefore rated as better by the patient, but not necessarily by the speech pathologist, who was more attuned to the absence of changes in quality.

TABLE 4. LARYNGEAL VIDEOSTROBOSCOPIC ASSESSMENT OF 15 CASES BY WILCOXON'S TEST OF MEDIAN EQUAL TO 0.000000 VERSUS MEDIAN NOT EQUAL TO 0.000000

		Estimated	
Parameters	*No. of Cases*	*p*	*Median*
Supraglottic hyperfunction	15	.001	1.000
Periodicity	14*	.281	0.000
Glottic gap	15	.001	1.000
Amplitude vibration	14*	.022	0.500
Mucosal wave	14*	.022	0.500
Symmetry	15	.234	0.500
Overall function based on above	15	.001	3.000

*One subject could not be rated on vibratory activity because of malfunction of strobe light, so that subject was rated only on supraglottic activity, glottic gap, and symmetry.

OBJECTIVE MEASURES

It is interesting that airflow significantly decreased for all three groups. Even more interesting is the observation that individuals with low preoperative flows increased flow following treatment. In other words, the treatment tended to normalize values. It was anticipated that increased glottic closure would result in increased intensity and an improved SNR, as proved true for all three disorder groups. It was also assumed that increased closure would result in better vocal control, less aerodynamic turbulence, and decreased perturbation values. Contrary to expectations, jitter and shimmer increased significantly, not only in the unilateral group but in the scarred group as well. The bilateral groups showed a similar response, but only shimmer was significantly changed.

Although laryngeal videostroboscopy is extremely useful in assessing disease and in observing the effect of treatment, it is difficult to objectively quantify these results to assess efficacy. It is possible to observe the effect of injection on vocal fold vibration and to determine the degree of correction of glottic closure; one can also grossly quantify the amplitude of vibration, mucosal wave, and periodicity. Unfortunately, it is difficult to mask the treated larynx because of the obvious displacement and whitish color often found in the injected fold. It is therefore not possible to objectively compare random preoperative and postoperative samples to eliminate judgment bias.

PHYSIOLOGIC ASPECTS OF COLLAGEN INJECTIONS

In addressing any particular type of disorder of the vocal fold, one must consider the components contributing to the dysphonia, including respiratory support and the vibratory structure. Often subtle changes in vocal fold composition affect vibratory properties, so that it is undesirable to lump all patients with paralysis or glottic insufficiency into the same group. For example, simply adding mass to a deficient vocal fold does not assure adequate vibration; in some instances it may increase stiffness and thereby impede vibration. The physical properties of GAX allowing superficial precise placement in focal defects and the biologic properties rendering it effective in the scarred larynx make collagen useful in addressing complex vocal fold problems associated with discrete tissue loss or scarring.

Resorption is reduced when collagen is injected into more superficial vocal fold levels (superficial lamina propria) and, in many patients, a superficially injected implant could be seen easily through the transparent mucosa years after injection. The recent use of GAX collagen has drastically reduced the amount of resorption,[25,26] but it may still occur in some patients. Usually it is very gradual and only minimal. In most of these patients, such resorption is not accompanied by a decrement in voice function. It is likely that some degree of resorption occurs in all patients, but this is quantitatively offset by deposition of host collagen. Functionally such change may be insignificant as long as the functional correction remains. Those patients who actually lose correction but maintain voice improvement deserve comment.

We hypothesize that the patient receives immediate relief after injection, and if the implant is properly placed in the lamina propria, gradual resorption and replacement allow the vocal mechanism to compensate incrementally for small changes. In other words, some neuromuscular retraining is occurring over time as the patient adjusts to these small changes, allowing the patient to hit the vocal target even with an inadequate vocal fold structure. This biologic successive approximation training is an example of alteration of the nervous system through biofeedback. Such nervous system plasticity may be an important mechanism in the success of collagen injection in some patients (H. Okamura, personal communication, 1989).

Reviewing selected patients' videostroboscopic studies reveals four patterns of change: 1) correction persists with negligible perceptible change, 2) correction decreases over the first few weeks and then stabilizes within 1 to 3 months, 3) correction persists months to years and then suddenly, usually after an upper respiratory tract infection, resorption occurs, and 4) rapid resorption occurs in a few patients within weeks. This last group consists mainly of patients with other medical problems such as Parkinson's disease. It is not totally clear why these patients are so resistant to correction. Problems with neuromotor control might explain their inability to adapt, but it is not at all clear why they should be susceptible to implant resorption.

In those patients for whom the implant persists but the contour or distribution is not ideal, it is possible to redistribute superficially placed collagen for several months after injection. In patients with less than ideal contour, voice, and stroboscopic findings following injection, visible collagen was nudged from an anterior to a more posterior location with the edge of the injection device; such procedures were done within 2 weeks of injection, by using topical anesthesia and indirect laryngoscopy in the outpatient clinic. In three patients we easily removed small focal blebs of injected collagen, within 1 year of injection, by placing a small incision over the collagen and aspirating with a small suction tip. No apparent scar tissue or inflammatory tissue developed, and in each case the voice improved with loss of diplophonia and decreased roughness.

No patients treated with GAX collagen injection experienced airway compromise, focal redness, swelling, or other signs of allergic reactions. Delayed onset of erythema at the injection site in two patients — one of whom also developed redness at the skin test site — occurred early in our series when Zyderm (not GAX collagen) was used. Overall, GAX preparations are less antigenic and persist longer.[37] Zyderm, Phonagel, and Zyplast are qualitatively different from other available forms of collagen (Koken Atelocollagen, Gelfoam, Collastat, and Avitene), and their biologic characteristics seem most favorable for vocal fold injection.[34] Other studies may not be comparable if different materials are used for injection.

ROLES OF COLLAGEN

Factors that determine the efficacy of collagen injection include the degree of glottic insufficiency and the specific vocal fold disorder. In some instances conditions may be best treated by combining collagen injection with other modalities such as thyroplasty. Our experience suggests that collagen injection may be used to treat many different conditions, but it is particularly useful in four situations.

Atrophied Vocal Fold. Examples include patients with high vagal lesions showing loss of recurrent and superior laryngeal nerves, presbylaryngis with loss of vocal fold connective tissue bulk and a characteristic arrowhead-shaped residual glottic gap during phonation, congenital hypoplasia in which there is failure of development of the layers of vocal fold such as in sulcus vocalis, and isolated superior laryngeal nerve paralysis. In all of these examples there is loss of fullness of the vocal fold, often associated with a medial furrow. Since collagen can be injected effectively in a superficial plane, it is possible to fill out such folds and recontour the vocal fold to match the contralateral side.

Scarred Vocal Fold. Scarring of the membranous vocal fold is a difficult problem, because the functional integrity of the tissue is destroyed, and even with perfect displacement, restoration of vibratory activity will not occur unless the tissues undergo some biologic transformation. No procedure or material besides collagen has been shown to address this problem. Collagen injection has been demonstrated to soften scar tissue in the dermis[38] and also in vocal folds.[33] Such changes have allowed for additional augmentation and restoration of the body-cover relationship required for vocal fold vibration. This effect of collagen is based theoretically on the biologic activity of the implant affecting the scar tissue–amino acid equilibrium to allow remodeling over time. Unfortunately, it is difficult to inject anything into scar tissue, and optimal results may take many injections over several years. For now, there are no suitable alternatives.

Minimal Glottic Insufficiency. In patients with relatively minimal glottic insufficiency who are bothered by weak, breathy voice production, collagen injection has proven a relatively safe and successful method of treatment. Many patients with presbylaryngis, with bilateral paresis from neurologic disease or trauma, and with bowing due to cricothyroid muscle weakness fit in this group. We found that small amounts (0.05 to 0.20 cm^3) of GAX collagen injected in the plane of the vocal ligament and the intermediate layer of the lamina propria were successful at producing improved voices.[32] These cases may represent instances in which some gradual resorption occurs as the patient develops improved phonation strategies.

Focal Vocal Fold Defects and Adynamic Segments. Focal loss of tissue or scarring confined to a limited area of the membranous vocal fold requires precise placement of a filler substance. Often the scarring may be so subtle as to escape detection on routine examination but will appear as an adynamic segment, with absence of a mucosal wave, on laryngeal videostroboscopy. Collagen can be injected with extreme precision at the site of the defect in mucosal and immediate submucosal tissues. This is a unique advantage over Teflon, which must be injected deep into the thyroarytenoid muscle.

Each of the four conditions can coexist with additional vocal fold disease that might be more suitably handled with a different form of treatment such as thyroplasty, reinnervation, or arytenoid adduction. In some of these instances, collagen injection might be considered as an adjunctive measure.

In addition to patient selection, the most important factor in determining the success of collagen injection is proper technique. All those who have reported successful management of glottic insufficiency by collagen injection have described placement of the implant at a superficial level in the vocal fold. This is quite different from the placement of Teflon. Deep injection of collagen results in poor correction of the defect and rapid resorption of the implant. If the material fails to be distributed as intended, it is possible to modify the contour by rubbing the edge of the vocal fold with the injector device. Scarred vocal folds may require injection at different levels to facilitate maximal distribution of the implant.

SUMMARY AND CONCLUSIONS

This study and other clinical data indicate that collagen injection is relatively safe and useful in treating atrophic, scarred, or focally damaged vocal folds, and that it is helpful in relieving symptoms in patients with a small degree of glottic insufficiency. Some conditions treatable with collagen cannot be handled effectively with other treatment modalities, and other conditions might benefit from collagen injection as an alternative or adjunctive measure. While there is no reason to claim that collagen injection is the single best treatment for glottic insufficiency, these data support inclusion of GAX collagen injection in the armamentarium of the phonosurgeon engaged in treating glottic insufficiency problems. Collagen differs from other injectables in that it is a bioimplant with the capacity to be assimilated into the host tissues and soften scar tissue. A collagen implant can be redistributed or removed after injection without harmful effects. No patients have exhibited allergic reactions to the newer GAX collagens (Zyplast or Phonagel).

Acceptance, however, has been hampered by concerns over safety and efficacy that do not seem justified on the basis of worldwide experience and the data presented in this study. Ironically, Gelfoam has never been approved by the FDA for laryngeal injection, and yet it is commonly injected into vocal folds by laryngologists to determine if a patient is a suitable candidate for Teflon injection.

A GAX collagen generically identical to Zyplast is commercially available, but use in the larynx has not been approved.

The immediate challenge is to make collagen injection available to patients in need. Collagen injection has been studied more extensively than many other currently used substances. Our results on 119 patients showing it to be relatively safe, well tolerated, and effective are consistent with those of other researchers. Collagen can be used to treat a variety of conditions for which there are no good alternatives, and it can be considered a useful adjunctive measure in treating complex vocal fold problems.

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EXPERIMENTAL OTITIS MEDIA EVALUATED BY MAGNETIC RESONANCE IMAGING: AN IN VIVO MODEL

KENNY H. CHAN, MD
PITTSBURGH, PENNSYLVANIA
J. DOUGLAS SWARTS, PHD
PITTSBURGH, PENNSYLVANIA
YOSHIE HASHIDA, MD
PITTSBURGH, PENNSYLVANIA
WILLIAM J. DOYLE, PHD
PITTSBURGH, PENNSYLVANIA
DAVID KARDATZKE
PITTSBURGH, PENNSYLVANIA
GERALD L. WOLF, PHD, MD
BOSTON, MASSACHUSETTS

The use of magnetic resonance imaging in otitis media research is being explored in our laboratory. In this study, we present a new method for studying changes in the middle ear cleft due to an episode of induced otitis media in the chinchilla model. It uses gadolinium–diethylenetriamine pentaacetic acid, a magnetic resonance imaging contrast agent, to examine the uptake and washout characteristics of middle ear mucosa during an inflammatory episode. Parameters such as the time to maximum intensity of the mucosa and the washout rate of the contrast agent from the mucosa were significantly correlated to the duration of the infection.

KEY WORDS — animal model, inflammation, magnetic resonance imaging, otitis media.

INTRODUCTION

The use of magnetic resonance imaging (MRI) to assess the middle ear (ME) space in animal models has been previously reported by our laboratory.[1] It was noted that MRI is more accurate than tympanometry in assessing the ME space. Furthermore, MRI enhanced by gadolinium–diethylenetriamine pentaacetic acid (Gd-DTPA; Magnevist) allows excellent visualization of the ME mucosa. The potential of this imaging technique, beyond high-resolution images, was suggested.

In the pathogenesis of otitis media (OM), inflammatory changes of the ME mucosa resulting from noxious agents are a prominent feature. Studies of inflammation as assessed by MRI have been performed. An experimental model of chemically induced soft tissue inflammation evaluated in vivo by MRI in rats was reported.[2] Edematous foci were detected in T2 spin-echo (SE) scans as well as T1-weighted SE images using Gd-DTPA. The inflammatory response of the human sinonasal tissues evaluated by means of MRI has also been addressed.[3,4]

Traditionally, OM research involving animal models evaluates the host's acute and chronic inflammatory reaction to a noxious event by use of biochemical, bacteriologic, or histologic methods.[5] The first two types of assay are in vitro procedures in which the effusion must be removed from the animal for analysis. This type of analysis assesses the cumulative events of the inflammatory process at selected points in time, but is incapable of providing real-time information. The last assay method requires that the animal be killed and examined ex vivo. This model eliminates the possibility of repeat assessment or modification of the response in a particular animal. The ability to study the ME in vivo could overcome some of the shortcomings of the traditional methods. In this paper, we present a method for studying the ME mucosa in vivo by using Gd-DTPA–enhanced MRI. This method is based on the mucosal uptake and washout of the contrast agent Gd-DTPA. Stages of the inflammatory process, observed by Gd-DTPA–enhanced MRI, were correlated with findings of histologic analysis to validate this method.

METHODS

Our previous experience indicated that Gd-DTPA could be detected in the chinchilla ME mucosa shortly after intravenous injection. However, no quantitative information was available describing the uptake and washout characteristics of Gd-DTPA for ME mucosa or effusions. This study was performed in two phases. In the first phase, two pulsing sequences for studying the uptake and washout of Gd-DTPA from the ME mucosa were evaluated. The domestic cat (*Felis catus*) was chosen for this portion of the study. In the second phase the chinchilla (*Chinchilla laniger*) model was used in a comparison of the degree of inflammation, as defined by the previously established imaging protocol, to the duration of the infection, and to the preliminary results of light microscopic histologic analysis.

Phase 1. Since the uptake rate of Gd-DTPA in the ME mucosal surface had not previously been ascertained, imaging at high rates was necessary to determine whether slower imaging sequences would

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From the Departments of Otolaryngology (Chan, Swarts, Doyle, Kardatzke) and Pathology (Hashida), Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, and the Center for Imaging and Pharmaceutical Research, Massachusetts General Hospital, Boston, Massachusetts (Wolf). This study was supported in part by grants from the National Institutes of Health (DC00158 and DC00561) and the Otitis Media Research Center. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Children's Hospital of Pittsburgh.

REPRINTS — Kenny H. Chan, MD, Dept of Otolaryngology, Children's Hospital of Pittsburgh, 3705 Fifth Ave at DeSoto St, Pittsburgh, PA 15213.

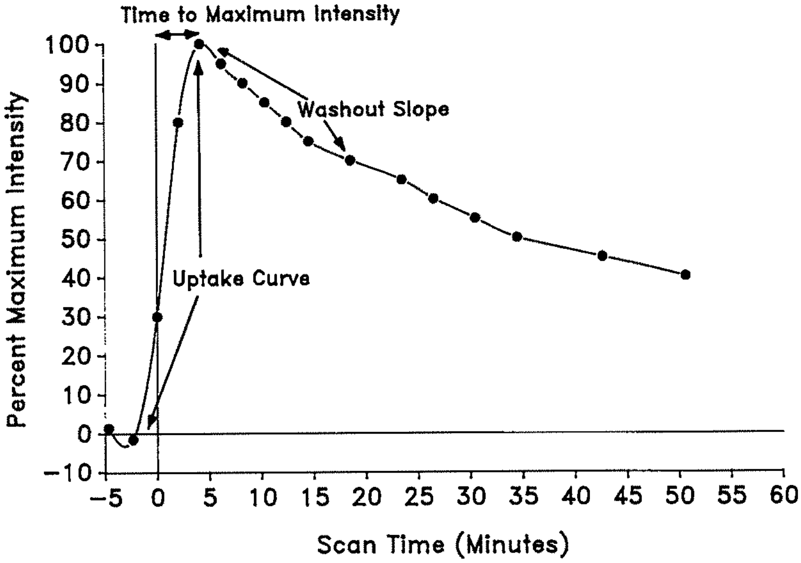


Fig 1. Idealized uptake washout curve illustrating variables discussed in text.

obscure significant aspects of this temporal process. A comparison between fast low-angle sequences (FLASH; TR = 100 milliseconds, TE = 13 milliseconds, slice thickness 5 mm, two excitations, matrix = 192 x 128)[6] and T1-weighted SE sequences (TR = 400 milliseconds, TE = 25 milliseconds, slice thickness 5 mm, two excitations, matrix = 192 x 128) was made.

Two female domestic cats (average weight 3.2 kg) were scanned; their eustachian tubes had been unilaterally obstructed by Silastic sponges and they had had a stable unilateral ME effusion for more than 4 months. The animals were sedated with ketamine hydrochloride and acepromazine maleate (100:1) at 10 to 15 mg/kg. An intravenous catheter was inserted and sedation was maintained through periodic doses of pentobarbital at 5 to 10 mg/kg. The animals were placed prone in a 1.5-T MRI unit (Signa, General Electric). A Gd-DTPA reference source (0.68 mol/L) was taped to the dorsal surface of the animal's head, which in turn rested on a 7.62-cm surface coil. Following intravenous injection of Gd-DTPA (100 μmol/kg) one animal underwent 13 sequential FLASH scans in 7 minutes and the second animal underwent T1-weighted SE scans, for a total of 19 scans in 40 minutes.

Phase 2. The resolution of an induced episode of OM in the chinchilla model, determined histopathologically, was reported to be about 6 weeks.[7] In 25 chinchillas (average 500 g), unilateral acute OM was induced by inoculating 250 to 500 colony-forming units of *Hemophilus influenzae* by the transbullar approach. The time points at which scanning was performed — that is, days postinfection — and the respective numbers of animals (in parentheses) were as follows: 3 days (four), 6 days (five), 9 days (five), 12 days (four), 16 days (three), 21 days (two), and 28 days (two).

Prior to MRI scanning animals were sedated with ketamine hydrochloride (20 mg/kg) via the subcutaneous route, supplemented with pentobarbital (10 mg/kg) via the intraperitoneal route. Under satisfactory sedation, a femoral vein catheter was inserted by means of the operating microscope. Supplemental sedation and the introduction of Gd-DTPA were via this route. The animals underwent sequential T1-weighted SE MRI. Each scanning session consisted of two baselines, a Gd-DTPA injection, and sequential scans at 3-minute intervals for at least 30 minutes. On completion of scanning, the animals were killed by barbiturate overdose. Their bullae were removed, fixed in 10% formalin, and decalcified in 5% formic acid. Thin sections of both the infected and uninfected bullae were stained with hematoxylin and eosin and studied under light microscopy. Measurements of ME mucosal thickness were made with an image analysis package (American Innovision V150).

Data Acquisition and Analysis. Intensity values were determined by the resident software of the scanner for the chosen region of interest (ROI). The ROI for ME mucosa was generally composed of four pixels, whereas that of the ME effusion and the Gd-DTPA reference was larger. A pixel is the two-dimensional representation of the smallest recognizable volume as determined by the scanning parameters: field of view, matrix size, and slice thickness. For the scanning parameters used in this study, the smallest volume that can be resolved is 0.586 mm^3 (slice thickness = 3 mm, field of view = 8 cm, matrix = 256 x 128).

The uptake and washout rates of Gd-DTPA for the mucosa and effusion are presented as a time-activity curve defined by plotting MRI intensity as a function of time (Fig 1). To produce these curves, variation in peak intensity was standardized by subtracting the average baseline intensity of the ROI, before Gd-DTPA injection, from the intensity val-

SIMPLE CORRELATION COEFFICIENTS AND P VALUES

	All Observations					*First 16 Days*				
	N	*Pearson* R^2	*p*	*Spearman* R^2	*p*	*N*	*Pearson* R^2	*p*	*Spearman* R^2	*p*
Days postinfection										
Baseline intensity	25	.26	.2	.18	.4	21	−.03	.89	−.01	.95
Maximum intensity	25	.29	.15	.28	.17	21	.1	.67	.08	.72
Time to maximum intensity	25	.55	*.004*	.63	*.0007*	21	.55	*.009*	.54	*.01*
Slope washout curve	25	.43	*.03*	.5	*.01*	21	.62	*.003*	.58	*.006*
Slope effusion uptake	25	.53	*.007*	.44	*.02*	21	.7	*.0004*	.7	*.0004*
Mucosal thickness	22	.56	*.006*	.51	*.01*					
Log mucosal thickness	10	.77	*.009*	.72	*.02*					
Mucosal thickness										
Baseline intensity	12	−.09	.78	−.11	.75					
Maximum intensity	12	.038	.91	.38	.22					
Time to maximum intensity	12	.339	.28	.39	.21					
Slope washout curve	12	.087	.788	.326	.3					
Slope effusion uptake	12	.51	*.09*	.74	*.006*					
Log mucosal thickness										
Baseline intensity	10	.04	.9	−.018	.96					
Maximum intensity	10	.2	.58	.52	.11					
Time to maximum intensity	10	.29	.41	.26	.48					
Slope washout curve	10	.07	.84	.1	.78					
Slope effusion uptake	10	.63	*.05*	.72	*.02*					

Italics indicate significance.

ues following Gd-DTPA injection and expressing this value as a percentage of the corrected maximum intensity. From these time-activity curves the parameters discussed in this paper were determined.

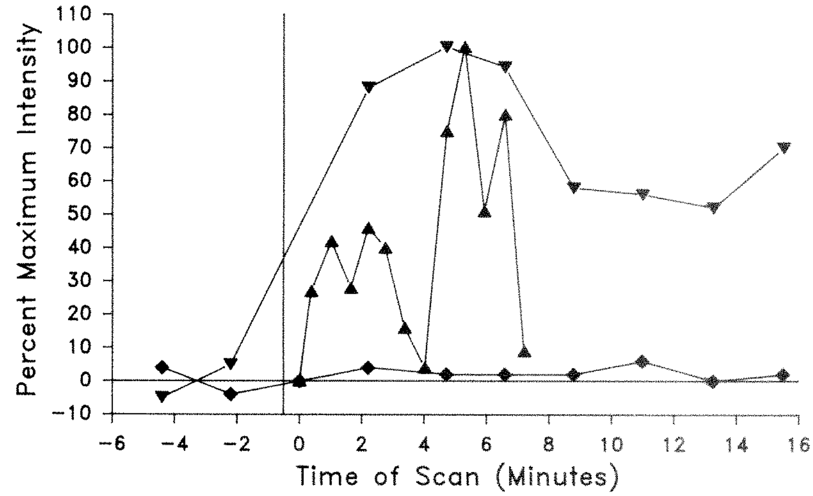
The data were analyzed to determine whether a relationship exists between the duration of an infection, as an index of disease, and the following variables: raw baseline mucosal intensity, raw maximum mucosal intensity, time to maximum intensity, slope of washout curve, and rate of accumulation of contrast in the effusion. A second series of comparisons was also performed between these variables and mucosal thickness as measured from histologic slides. Slopes of the washout curves were calculated and the Pearson and Spearman correlation coefficients were determined. The graphs depict the Pearson correlation coefficients for each animal, those for each variable, and the least squares fit line and 95% confidence intervals through these data. In several instances two least squares fit lines are presented, one for all the data and the other for a subset of data encompassing the first 16 days of the infection. For the Table a p value less than .05 indicates that the correlation is significantly different from zero.

Measurements of mucosal thickness at 10 regions of interest, including the margins and septa of the bulla, were taken from histologic sections. For each region a circle of random radius was drawn by the computer. The intersection of this circle with the mucosa dictated the thickness to measure. The mucosal thicknesses of four regions along the superior boundary of the bulla were used in this analysis, because they correspond to the region from which the mucosal intensity values were obtained.

RESULTS

With the use of the Gd-DTPA reference, it was

Fig 2. Comparison of standardized time-activity curves for mucosa generated with fast low-angle sequences (▲), and T1 spin-echo (▼) techniques. Superimposed are Gd-DTPA reference source intensity values (diamonds) indicating relative stability of magnetic resonance signal during one scanning session.



determined that the intensity values obtained during sequential scanning remained relatively constant (Fig 2, diamonds). This finding eliminated scanner variation as the source of the observed changes in the ROI intensity value following Gd-DTPA injection. This procedure was performed in over half of the animals before it was excluded.

Figure 2 also shows a comparison of the time-activity curves generated by FLASH and SE MRI of the ME mucosa from the two cats during phase 1 of the study. The curves have been superimposed to demonstrate that the peak intensity following Gd-DTPA occurred approximately 4 to 5 minutes following injection. Because of the limited anatomic information from the FLASH technique and since the uptake portion of the activity curve was fully captured by the SE sequence, it was concluded that the latter technique can adequately image the ME mucosa.

The chinchilla ME mucosa was found to behave in a manner similar to that of the cat mucosa following injection of Gd-DTPA; both the uptake and washout arms of the time-activity curve were observed in all animals. Figure 3 presents two images that illustrate the increase in mucosal intensity above baseline following the injection of Gd-DTPA (Fig 3B). Figure 4 shows examples of time-activity curves for three representative animals scanned on days 3, 6, and 9 postinfection. These time-activity curves demonstrate the differences in the uptake and washout of Gd-DTPA. The uptake portions of the curves are equally steep for the animals infected 3 and 6 days prior to scan. The animal infected 9 days before scanning shows a shallower uptake curve. In the analysis of the time-activity data, it became evident that the washout portions of the curves are nonlinear; this finding suggests that at least two processes are responsible for the elimination of Gd-DTPA from the mucosa. In an attempt to differentiate between these effects, only the first 20 minutes of data following maximum intensity was used to calculate the slope of the washout portion of the time-activity curve. The Gd-DTPA washout rate decreased and was inversely related to the duration of the infection. The only parameters not illustrated in Fig 4 are the raw baseline and raw maximum intensities.

For the initial analysis of the time-activity curves, days postinfection was used as the independent variable. A significant relationship was found between days postinfection and 1) the time to maximum in-

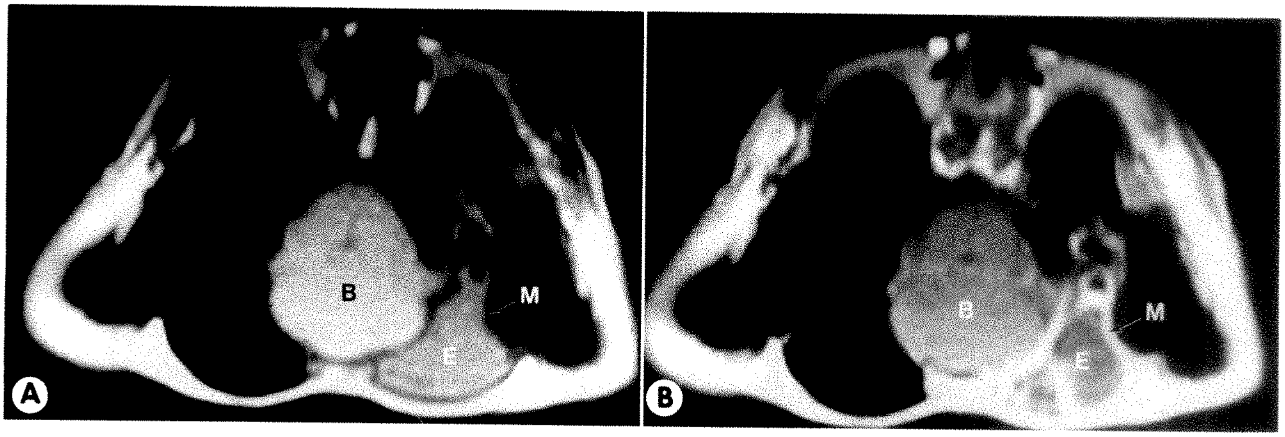


Fig 3. Magnetic resonance images illustrating change in chinchilla mucosal intensity A) at baseline and B) after bolus injection of Gd-DTPA. Intensity of mucosa (M) of infected left side increases dramatically. E — effusion, B — brain.

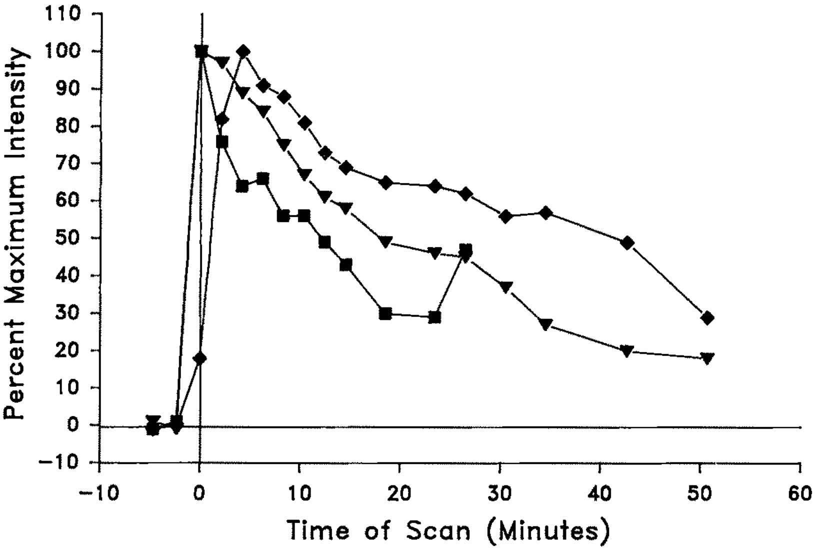


Fig 4. Standardized time-activity curves of middle ear mucosa of representative chinchillas 3 days (squares), 6 days (triangles), and 9 days (diamonds) postinfection. As duration of infection increases, there is decrease in uptake slopes, increase in time to maximum intensity, and decrease in washout rate.

tensity (Fig 5A), 2) the slope of the washout portion of the curve (Fig 5B), and 3) the uptake slope of the effusion (Fig 5C). There was no correlation between days postinfection and raw baseline mucosal intensity or maximum intensity. Correlation coefficients for the first 16 days postinfection are larger than those obtained for the entire data set. This finding suggests that healing processes may begin after about 2 weeks. Histologic mucosal thickness was found to be directly and significantly related to the duration of the infection (Fig 6). These variables, the simple regression coefficients, and associated p values are listed in the Table.

Longitudinal histopathologic changes of the ME mucosa subsequent to a bacterial infection in the chinchilla model were first described by Juhn et al.[7] Inflammatory characteristics of both acute and chronic infection were seen throughout this study. There were the less dramatic microscopic findings such as changes in the cellular infiltrates from a predominately neutrophilic population to a lymphocytic one, the increase in both the caliber and the number of subepithelial capillaries, the formation of granulation tissue, and the appearance of neoosteogenesis. The most striking change during the course of disease, almost visible without magnification, was the increase of ME mucosal thickness. The average mucosal thickness changed from a baseline of 11 ± 6 μm to 1,142 ± 1,126 μm at 28 days postinfection (Fig 6).

Using histologic mucosal thickness as another measure of disease severity, we computed a second set of correlations. Of the parameters significantly correlated with days postinfection, only the uptake slope of the effusion was significantly correlated to mucosal thickness. Time to maximum intensity and the slope of the washout curve were at best poorly correlated to mucosal thickness. Because there is such a broad range of mucosal thicknesses (10 to 1,500 μm), this variable was logarithmically transformed and the regressions rerun. This strengthened the relationship between mucosal thickness and days postinfection. Despite this transformation, none of the previously insignificant comparisons reached significance. Baseline intensity and maximum intensity remained poorly correlated to both mucosal thickness and its logarithm. Although these correlations were insignificant, the correlation between the logarithm of mucosal thickness and maximum intensity ($r = .52$) was of the same magnitude as many of the significant correlations. The lack of significance may be due to low power, a consequence of the small sample size ($N = 10$). Despite the fact that several of the characteristics of the time-activity curves and mucosal thickness are significantly correlated to days postinfection, these parameters were not significantly correlated to one another.

DISCUSSION

A unique in vivo method for studying OM by relying on real-time information derived from MRI has been described. Using Gd-DTPA as a tracer, we characterized the behavior of the ME mucosa during a course of induced OM. Observed changes in mucosal intensity, following a bolus injection of Gd-DTPA, were not due to variability in the scanning equipment. Significant correlations exist between the duration of the infection and the time it takes to reach maximum intensity and between this duration and the rate at which the contrast agent diffuses out of the mucosa. No significant relationship exists between the duration of an infection and the raw mucosal baseline or maximum intensity values. Although a significant correlation exists between mucosal thickness and days postinfection, similarly strong relationships do not exist between mucosal thickness and the various parameters of the Gd-DTPA curves, except for the uptake of Gd-DTPA by the effusion.

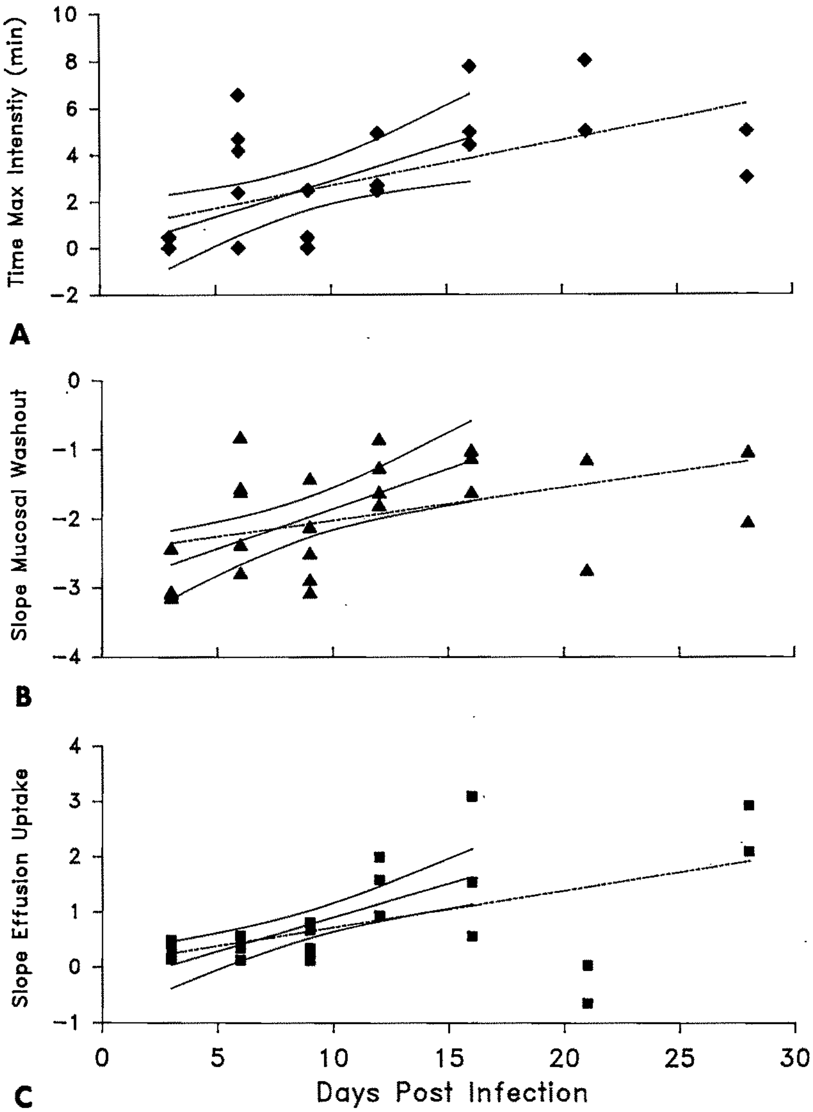


Fig 5. Correlations between days postinfection and A) time to maximum intensity, B) slope of washout portion of mucosal time-activity curve, and C) slope of effusion uptake curve. Data points for individual animals are indicated. Best-fit line (solid) and 95% confidence interval for data up to 16 days postinfection are presented. Dash-dotted line is best fit for all data.

The interpretation of the observed changes in the intensity values requires an understanding of not only the pathophysiology of the ME mucosal system, but also contributing factors of the MRI process and the pharmacokinetic properties of the contrast agent. Given standardized scanning parameters, the intensity of a pixel, representing a voxel (imaged volume), is dictated by two factors: the proportion of the voxel that generates signal and the strength of signal generated. The need to control

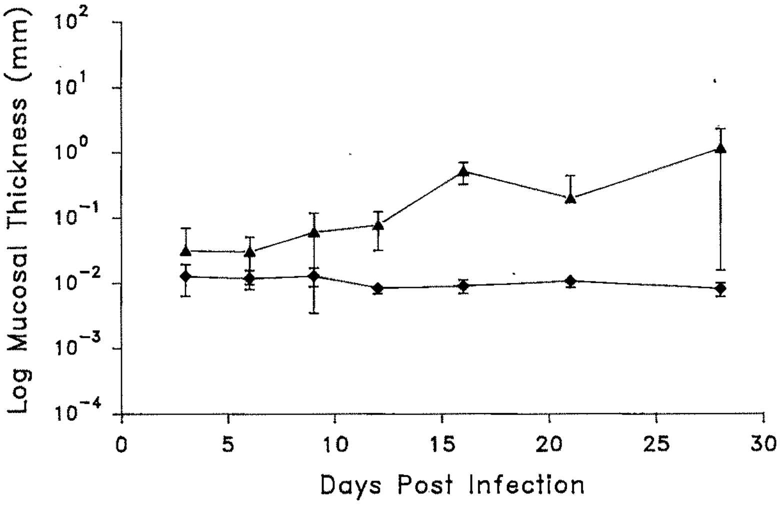


Fig 6. Means and standard deviations of middle ear mucosal thickness from infected (triangles) and control (diamonds) bullae during 28 days of induced episode of otitis media. Mucosal thickness changed from baseline of 11 μm to 1,142 μm at 28 days postinfection.

partial volume effects becomes essential when the voxel is not completely filled during the early stages of a course of experimental OM. Subtraction of the baseline pixel intensity values from those following Gd-DTPA injection standardizes for this effect. This procedure also eliminates the confounding effects of mucosal composition on intensity. If the volume included within a voxel contributed to intensity in only these ways, its input to the total signal could be eliminated. However, physiologic processes that are responsible for the accumulation of Gd-DTPA in the mucosa may also affect its intensity.

Pathophysiologic parameters that may affect pixel intensity include the rate of perfusion and differences in the vascularity and permeability of the submucosal capillaries. These factors determine the amount of contrast agent available to the ME mucosa and the ease with which it passes into the extracellular space and hence into an effusion. Generally, given a constant bolus size, the observed changes in intensity will be proportional to the concentration of Gd-DTPA that is retained in the mucosa or effusion. Because normal mucosa is so thin and its capillaries are relatively impermeable to Gd-DTPA, the increase in pixel intensity due to the presence of the contrast agent is negligible. Changes in the mucosa due to infection allow high Gd-DTPA concentrations to develop, thus affecting pixel intensity. The rate at which the maximum intensity is reached and the persistence of this intensity are correlated with the duration of infection. Whether these changes reflect the increased volume of the mucosa or are in part dependent on alterations in its vascularity and the permeability of its capillaries remains to be delineated. Clearly, the most interesting and potentially useful situation would be to find that correlations between intensity and measures of permeability and vascularity explain a significant portion of the variability observed in the system.

This method opens a new avenue in the investigation of OM pathogenesis using animal models. Further investigation focused on mucosal vascular permeability is being conducted. Clearly, this model can be extended to other mucosal-lined systems. A clearer understanding of OM pathogenesis will likely modify treatment plans and clinical response.

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SLOW CUMULATIVE EYE POSITION TO QUANTIFY OPTOKINETIC AFTERNYSTAGMUS

TIMOTHY C. HAIN, MD
CHICAGO, ILLINOIS

GAURANG PATEL
BALTIMORE, MARYLAND

In 30 normal subjects we computed the slow cumulative eye position (SCEP) of optokinetic afternystagmus (OKAN) that followed 60 seconds of full-field optokinetic stimulation at 60°/s. The mean SCEP was 112.8° ± 65.0°. The lower and upper fifth percentile limits for directional preponderance of the SCEP were −38.8% and 44.3%, respectively. The time constant, which we calculated by dividing the SCEP by the initial velocity, was 12.0 ± 7.4 seconds. This value is nearly identical to the time constant obtained from semilogarithmic regression of the decay of OKAN slow-phase velocity versus time. We conclude that the SCEP is a good measure of OKAN and that it reflects the substantial amount of variability and directional asymmetry observed in the optokinetic responses of normal subjects.

KEY WORDS — humans, optokinetic afternystagmus, optokinetic nystagmus.

INTRODUCTION

Optokinetic afternystagmus (OKAN) is the nystagmus that follows optokinetic stimulation. It is strongly affected by vestibular lesions in experimental animals[1-3] and is used as an aid in the diagnosis of vestibular lesions in some clinical laboratories. Our purpose in this report is to indicate the advantages of the slow cumulative eye position (SCEP) over other parameters used for characterization of OKAN, and to present normative data on the SCEP that were derived from 30 subjects.

Several technical problems should be considered in the measurement of OKAN.

1. In humans, OKAN is low in amplitude, with mean peak slow-phase velocities typically reaching only about 10°/s.[4,5]
2. The amplitude of OKAN has substantial variability in the same individual from trial to trial. The mean coefficient of variance of the initial slow-phase velocity of OKAN is about 35%.[5]
3. Decay of OKAN follows a complicated time course.[6-8]

The first two problems can be resolved by means of averaging techniques as described elsewhere.[5,9] Quantifying the complicated time course of OKAN entails curve-fitting, and there is no consensus as to the best procedure. Experimental evidence indicates that after a period of constant-velocity optokinetic stimulation, the decay of OKAN slow-phase velocity in humans has multiple exponentially declining components.[7,10,11] These components are described mathematically by the formula

$$\dot{e} = \mathrm{P0} \times \exp\frac{-t}{\mathrm{Tp}} + \mathrm{O0} \times \exp\frac{-t}{\mathrm{To}} + \mathrm{A0} \times \exp\frac{-t}{\mathrm{Ta}} + \mathrm{S0} \qquad (1)$$

Equation 1 describes eye velocity ($\dot{e}$) as a function of time (t) by means of three exponential terms and one constant term. Each exponential term has two parameters, one designating an initial value, and the other, a time constant of decay. Table 1[5,9,12-15] gives values of the exponential parameters for drum rotation at 60°/s for 60 seconds for normal subjects.

The first exponential term, the pursuit term, consists of rapidly decaying slow-phase eye velocity directed toward previous drum motion. It probably represents the sum of two processes, namely, smooth pursuit and a separate, rapidly decaying component of optokinetic nystagmus. The symbol P0 indicates the initial velocity, and Tp indicates the time constant. It is unclear whether measurement of the pursuit term is useful for diagnosis of vestibular disorders.

The second exponential term, or primary OKAN,

TABLE 1. NORMAL OPTOKINETIC AFTERNYSTAGMUS PARAMETERS REPORTED PREVIOUSLY

Reference	*P0*	*Tp (s)*	*O0*	*To (s)*	*A0*	*Ta (s)*	*SCEP (°)*	*n**
Tomlinson et al[14]				5				6
Tijssen et al[5]			11	11				30
Segal and Liben[9]			10	10				6
Dizio and Lackner[15]				7				20
Brandt et al[12]			15	12	4	50	137	5
Lafortune et al[13]	50	0.75	10	25			70	8

Values attributed to Brandt et al were computed from their data as indicated in text. Values attributed to Lafortune et al were estimated from their Figs 2-4. Value attributed to Dizio and Lackner was obtained by averaging together values reported for young and elderly subjects.

Abbreviations are defined with equation 1 and in paragraphs immediately following.

*Number of subjects studied.

From the Departments of Neurology and Otolaryngology, The Johns Hopkins University School of Medicine, Baltimore, Maryland. Supported by research grant NS00914 from the National Institutes of Health/US Public Health Service.

REPRINTS — Timothy C. Hain, MD, Dept of Neurology, Northwestern Memorial Hospital, Passavant 10, Superior and Fairbanks, Chicago, IL 60611.

represents slowly decaying slow-phase eye velocity, also directed toward previous drum stimulation. The initial velocity is indicated by Oo, and the time constant by To. Both Oo and To are reduced by vestibular lesions, and registration of primary OKAN can assist in the diagnosis of vestibular disorders.

The third exponential term, the reversal phase, quantifies activity with slow-phase eye velocity directed oppositely to drum stimulation. The initial velocity (Ao) and the time constant (Ta) have never been measured explicitly, but these values can be estimated from other parameters. It is known that for periods of optokinetic stimulation up to 1 minute, the reversal phase persists about twice as long as primary OKAN but has only about one fourth the total amplitude.[12] From computer simulation it can be estimated that values of Ao ranging between 3°/s and 5°/s and values of Ta ranging between 40 and 50 seconds are needed to obtain these relationships. The reversal phase persists in patients with vestibular loss, who no longer have a primary phase of OKAN.[16]

The last term, the constant So, represents constant-velocity spontaneous nystagmus. Normal subjects with eyes open and head upright rarely have more than 1°/s of spontaneous nystagmus.[17] In patients with vestibular lesions, however, the slow-phase velocity spontaneous nystagmus often exceeds that of primary OKAN.

Because of the small size and erratic nature of the OKAN response, fits of OKAN decay to the seven-parameter model of equation 1 do not produce clinically useful information, and simplified models with fewer parameters are always used. The first simplification is to discard the reversal phase, because as mentioned above, there is evidence that the reversal phase is not strongly affected by vestibular dysfunction. The pursuit and spontaneous nystagmus terms are handled in a variety of ways by individual workers. Lafortune et al[4] and Jell et al[6,18] discard the spontaneous nystagmus term, So, and fit OKAN data to the remainder. The model that they use is represented by equation 2.

$$\dot{e} = \mathrm{Po} \times \exp\frac{-t}{\mathrm{Tp}} + \mathrm{Oo} \times \exp\frac{-t}{\mathrm{To}} \qquad (2)$$

With this four-parameter model one can compute values for both the pursuit component and primary OKAN from the same OKAN response. Unfortunately, this is a complex model to fit to an erratic signal such as OKAN, and it is apparent that any substantial amount of spontaneous nystagmus will produce spurious results. In normal subjects, for a 60°/s drum rotation, this use of this model to analyze data produces an initial velocity (Oo) of approximately 10°/s and a time constant (To) of approximately 25 seconds.[13]

Equation 3 is an expression for a simpler model that discards all but one exponential term. This model or a close variant has been used by most investigators studying OKAN.[5,9,14,15,19,20]

$$\dot{e} = \mathrm{Oo} \times \exp\frac{-t}{\mathrm{To}} + \mathrm{So} \qquad (3)$$

The three-parameter model of equation 3 has two advantages over the four-parameter model. First, regression curves of OKAN data to the three-parameter model are affected less strongly by the intrinsic variability of OKAN than are regressions to the four-parameter model. Second, because of its simplicity, equation 3 lends itself to manual analysis. On the other hand, the disadvantage of the three-parameter model is an intrinsic error related to discarding of the pursuit term. To avoid such an error, many workers omit analysis of the first 1 or 2 seconds of the OKAN response, knowing that it is contaminated by pursuit, and use only the remainder for the fit.[5,9,19] In normal subjects, this method produces estimates of 10°/s and 10 seconds for initial velocity and the time constant (To), respectively (Table 1). Shorter time constants (eg, 5 to 6 seconds) have been reported by workers who use data from the first second of OKAN.[14]

To summarize, the two methods of quantifying OKAN discussed so far produce similar values for the initial velocity (about 10°/s), but dissimilar values for the OKAN time constant (ranging from 5 to 25 seconds). In other words, time constant estimates of primary OKAN are model-dependent. It would be preferable to describe OKAN with parameters that are independent of the model.

The SCEP is a model-independent parameter, because it is calculated from a direct measurement. Alternative names given to the SCEP include total amplitude,[12,20] total deviation,[1] and cumulative eye displacement.[4] In considering the SCEP as a measurement of OKAN, it is helpful to consider how it is related to the model-dependent parameters described previously. Both the three-parameter and four-parameter models separate OKAN into sets of variables indicating amplitude (Oo and Po) and duration (Tp and Tc). The SCEP contains information on both amplitude and duration. For the three-parameter model, given that there is no spontaneous nystagmus, the relationship is particularly simple, because in this case the SCEP is the numeric product of initial velocity (Oo) and time constant (To). Equations 4a and 4b show the derivation of this formula.

$$\dot{e} = \mathrm{Oo} \times \exp\left(\frac{-t}{\mathrm{To}}\right) \qquad (4a)$$

$$\mathrm{SCEP} = \int_0^\infty \dot{e}\,dt = \mathrm{Oo} \times \mathrm{To} \qquad (4b)$$

A similar expression, with P x Tp added for the

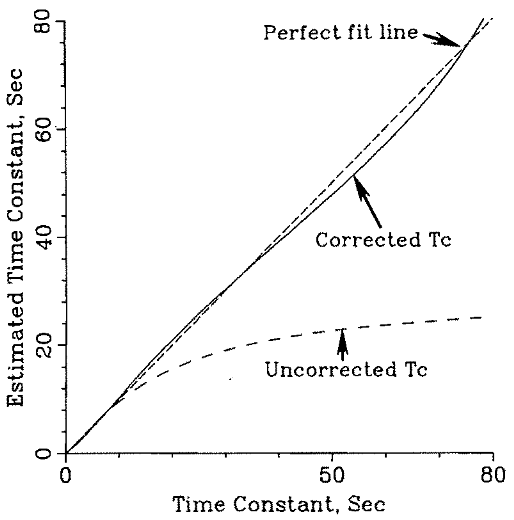


Fig 1. Relationship between estimated time constant calculated by slow cumulative eye position method (Uncorrected Tc, called Tc′ in text), estimate corrected by equation 5 (Corrected Tc), and true time constant.

pursuit term, is the equivalent for the four-parameter model.

Equation 4 suggests the possibility of calculating the time constant from the SCEP, by dividing the SCEP by the initial velocity. However, there is a practical problem. In the laboratory, the SCEP is calculated as a definite integral, with the limits of integration set by the duration of OKAN data collection. However, substitution of a definite integral for the infinite integral of equation 4 introduces error. When the time constant is long enough so that appreciable nystagmus persists beyond the upper limit of the SCEP integral, the effect of the error is to put a cap on the maximum time constant, which is the duration of the SCEP integral. To give an example, suppose that the time constant is very large, 1,000 seconds, and that the initial velocity is 10°/s. The SCEP over 30 seconds of the response is 300°, and the estimate of time constant would be 30 seconds. This cap may lead to erroneous results for some normal subjects.

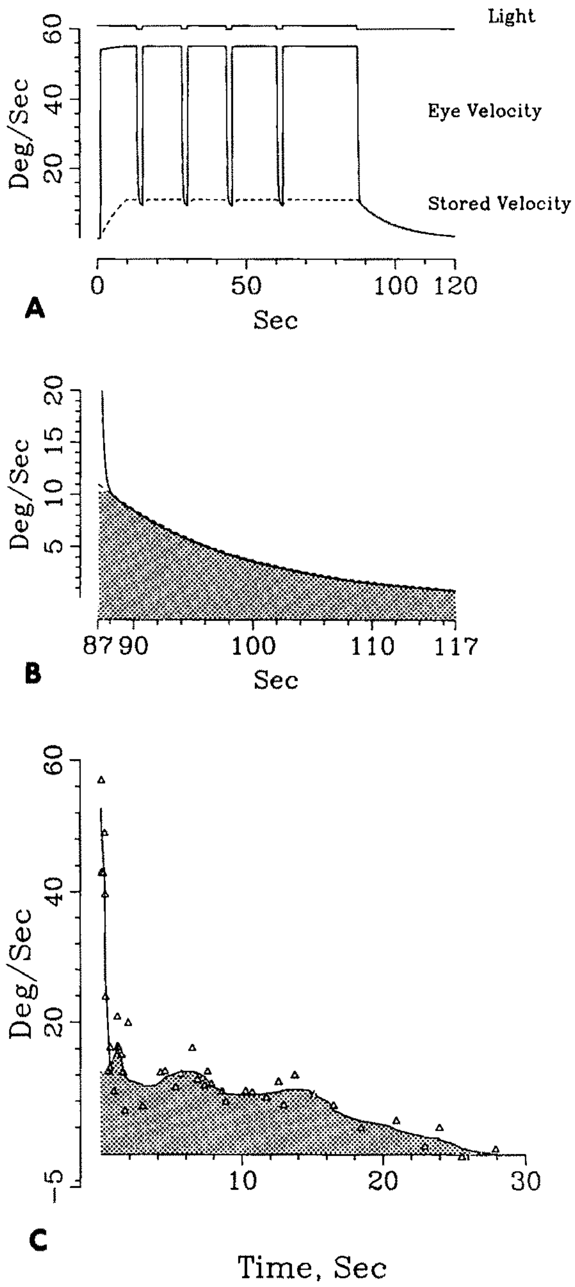


Fig 2. Illustration of method of calculating initial velocity, slow cumulative eye position (SCEP), and time constant. A) Slow-phase velocity profile of optokinetic nystagmus (solid line) and underlying optokinetic afternystagmus component (dotted line). B) Expansion of final portion of A, showing optokinetic afternystagmus decay curve and area included in SCEP integral (hatched). C) Slow-phase velocity tracing for normal subject. Solid line — smoothed slow-phase velocity, hatched area — portion of decay curve used for computation of SCEP.

This problem can be overcome if a correction formula is used. Figure 1 shows the relationship between the true OKAN time constant, Tc, and the time constant calculated from the SCEP, Tc′. Figure 1 was constructed from equation 4b according to the following procedure. For all time constants between 0 and 80 seconds, the SCEP was calculated from the definite integral of eye velocity between the limits of 0 and 30 seconds. The uncorrected time constant, Tc′, was computed by division of the SCEP by the initial velocity (set to 10°/s). Equation 5, below, was then derived from an asymptotic fit relating Tc′ to Tc (the given "true" time constant). The parameters of the fit were obtained by means of a numeric analysis method (Marquardt's procedure). Equation 5 provides a correction for values of Tc as large as 80 seconds, which correspond to values of Tc′ as large as 25 seconds. The performance of the correction formula is plotted as "Corrected Tc" in Fig 1. It should be noted that this formula applies only to SCEP data accumulated over 30 seconds.

$$Tc = -22.7 \times \ln\left(\frac{1.007 - Tc'}{25.5}\right) \qquad (5)$$

TABLE 2. NORMAL VALUES FOR SLOW CUMULATIVE EYE POSITION

	Mean	*SD*	*n*	*Lower 5%*	*Median*	*Upper 5%*
SCEP (°)	112.9	65.0	178	40.0	99.0	237.0
SCEPDP (°)	4.5	23.0	89	−44.3	−10.6	37.8
TcSCEP (s)	12.0	7.4	179	4.2	10.3	24.7
Tclog (s)	11.3	3.8	178	4.2	9.8	20.1

See text for abbreviations.

METHODS

We reanalyzed the OKAN data from the study of Tijssen et al[5] in order to develop normative values for the SCEP. These data were obtained from 30 normal subjects, who were evenly divided as to sex. Figure 2A shows the stimulus profile. In each trial, optokinetic nystagmus was elicited with a full-field optokinetic drum rotated at 60°/s for 60 seconds. During the stimulation the lights were switched off for 2 seconds at 12, 26, 40, and 60 seconds for sampling of the OKAN.[9] After the final sampling the lights remained off for 60 seconds, during which the data for the OKAN decay curve were collected. Another 60 seconds was allowed to elapse before the beginning of the next trial. Three trials for each direction were obtained from each subject.

Figure 2B,C shows the portion of the OKAN response from which we calculated the SCEP. Cumulative eye position was calculated by numeric integration of the area under the slow-phase velocity curve for the first 30 seconds, excluding the first 2 seconds; eye velocity going opposite to the drum was considered as zero. To this quantity, we added the initial velocity calculated from the initial samples, and multiplied by 2 seconds. The integration was performed according to the trapezoidal rule. We removed fast phases by using a manually assisted computer algorithm that considered direction, velocity, and duration of nystagmus. The initial velocity was calculated from mean slow-phase eye velocity during the second second after the lights were extinguished in the sampling periods. The directional preponderance of the SCEP (SCEPDP) was calculated from equation 6. (In equation 6, Right and Left indicate the magnitude of the SCEP to the right and left, respectively.) The time constant of decay of OKAN (Tc) was calculated by division of the SCEP by the initial velocity. The result was adjusted with the correction formula given in equation 5.

$$\text{SCEPDP} = 100 \times \frac{\text{Right} - \text{Left}}{\text{Right} + \text{Left}} \qquad (6)$$

RESULTS

Table 2 summarizes the results, including the SCEP, the SCEPDP, and the time constants calculated by the SCEP method. For comparison, time constants computed from the same data by semilogarithmic regression[5] are also shown. The distributions of all four measures of OKAN, which were based on individual trials of OKAN, were skewed significantly toward higher values. The significance of the skew was calculated from the third moment of the mean.[21] Because of the skew, the distribution is not "normal" in the statistical sense. Accordingly, we have provided fifth-percentile limits and median values, which were obtained directly from the frequency distribution histograms.

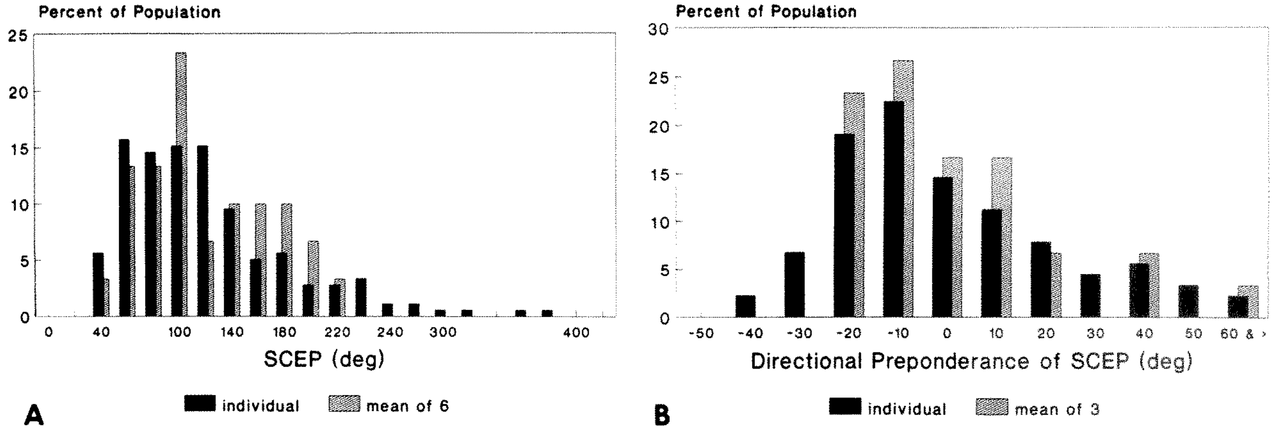
Figure 3A shows the distribution of SCEP for our 30 normal subjects. It shows both SCEP values computed from individual trials and values compared from the average of six trials for a given subject. The skewing of the distribution is reduced when trials are averaged. Figure 3B illustrates the distribution of the SCEPDP. Figure 3C is a plot of the time constant of OKAN computed both by the SCEP method and by semilogarithmic regression.

DISCUSSION

Our study provides normative data for the SCEP of OKAN. The mean SCEP obtained for our 30 subjects (112° ± 64°) is similar to results of other workers (Table 1). Brandt et al[12] reported a mean SCEP of 137° in 5 normal subjects. They continued the SCEP integration until the reversal phase started, rather than stopping the integration at 30 seconds as we did. This difference in technique may account for their slightly larger value. Lafortune et al[4] found an SCEP value of about 70° in 8 normal subjects. They included the reversal phase in their SCEP integral, and this may account for the smaller value that they obtained.

In spite of differences in method, the SCEP data are more consistent among laboratory groups than is the time constant of primary OKAN (To in Table 1). This consistency probably results from the procedure by which the SCEP is calculated — that is, the SCEP is measured directly from the OKAN profile and is not affected by the fitting function chosen to represent the response. Furthermore, for the most commonly used fitting function (the three-parameter model), one can describe the primary OKAN response completely by combining the SCEP and another directly measurable quantity, the initial velocity. The time constant of primary OKAN can also be calculated from the SCEP and the initial velocity by means of equations 4 and 5. However, because reported normal values for the time constant vary markedly among laboratories (Table 1), the SCEP is a better choice of descriptive parameter for OKAN.

We found that like the OKAN time constant and



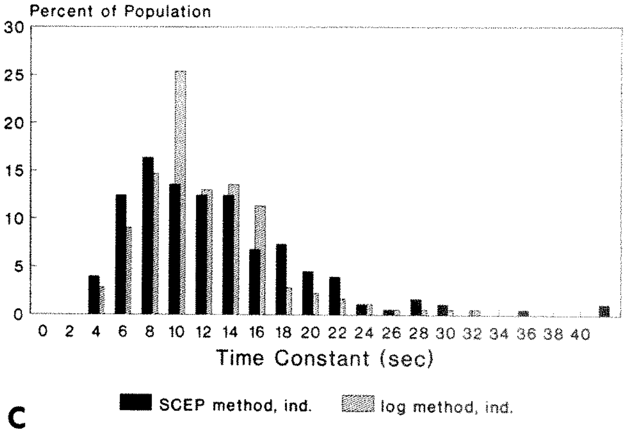


Fig 3. Distributions in 30 normal subjects. A) Of optokinetic afternystagmus slow cumulative eye position (SCEP). Solid bars — SCEP calculated from individual SCEP values (n = 178), hatched bars — SCEP calculated from average of six trials per person (three to left and three to right). B) Directional preponderance of SCEP. Solid bars — directional preponderance calculated from individual pairs of left-right trials, hatched bars — directional preponderance as calculated as difference between three trials to left and three to right, normalized to their sum. C) Optokinetic afternystagmus time constants. Solid bars — time constants calculated by SCEP method, hatched bars — time constants calculated by semilogarithmic fit.

initial velocity,[5] the SCEP can have a large directional preponderance in normal subjects. No other studies of directional preponderance of OKAN are available for comparison with our data.

For the purpose of defining normal OKAN and identifying vestibular abnormality, it is important to realize that the distributions of the SCEP and the time constant are both skewed in the normal population. There is an absolute lower limit (zero) for each, and the distributions are scattered toward higher values. Significant skewing was present for both methods of calculating the time constant. Analytically, it is easy to see why this might occur with the SCEP method. Consider the effect of a random deviation in initial velocity (Oo) that produces two estimates of initial velocity, Oo − delta and Oo + delta. Because the time constant (Tc) is proportional to 1/Oo, the errors in the time constant that correspond to the random deviations in velocity are distributed asymmetrically about Tc; this creates a skew. Because of the skewing, statistics that assume "normal" behavior in the mathematic sense do not apply. We recommend using percentile limits to separate normal from abnormal behavior, with percentiles calculated directly from the frequency distribution, as illustrated in Table 2.

Because of the skewing, comparisons among various methods of estimating OKAN parameters are difficult. Although the SCEP method of estimating the time constant had a larger SD than did the log-fit procedure, the lower fifth percentile limits were identical. As no disease has yet been identified in which the time constant of OKAN is abnormally long, the SCEP method could perform as well as the log-fit method for identification of pathologic abnormalities.

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FIRST INTERNATIONAL SKULL BASE CONGRESS

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LEPROMATOUS LEPROSY: NASAL MANIFESTATIONS AND TREATMENT WITH MINOCYCLINE

ANIL K. LALWANI, MD

THOMAS A. TAMI, MD ROBERT H. GELBER, MD

SAN FRANCISCO, CALIFORNIA

Nasal involvement in lepromatous leprosy is universal and occurs early in the course of the disease. Nasal symptoms include obstruction, crusting, bleeding, and hyposmia. Traditional therapy with dapsone, rifampin, and clofazimine is limited by its cost and toxicity. Minocycline hydrochloride, a tetracycline antibiotic with limited side effects, is promising as a new treatment for leprosy. A case is presented that highlights the clinical presentation, diagnosis, and treatment of lepromatous leprosy.

KEY WORDS — lepromatous leprosy, minocycline.

INTRODUCTION

Although uncommon in the United States, leprosy affects 12 to 15 million people worldwide and in many countries is the most common cause of chronic nasal symptoms.[1] Most physicians educated in the United States receive little or no training or clinical experience in the diagnosis and treatment of leprosy. In light of current trends toward an increasing immigrant population in the United States, the otolaryngologist must be familiar with leprosy and its recognition, diagnosis, and management. A recently encountered case of lepromatous leprosy (LL) highlights the clinical presentation, diagnosis, and treatment of this problem.

CASE REPORT

A 27-year-old Colombian immigrant reported a 6-month history of nasal stuffiness, nasal obstruction, and intermittent bloody discharge. He also described a 2-year history of decreased sensation in the hands and legs. Nasal examination revealed a large anterior septal perforation with surrounding granulation tissue, mucosal thickening, and crusting. The skin of the malar region and pinna was erythematous and ichthyotic. Hypertrophic scars were noted on the dorsum of the patient's hands and forearms (Fig 1). Neurologic evaluation demonstrated hypesthesia and anhydrosis in a glove and stocking distribution. Muscle strength was normal.

White blood cell count, differential count, electrolyte count, and liver function test results were normal. Urinalysis results were normal. The erythrocyte sedimentation rate was elevated at 39 mm/h (normal range, 0 to 15 mm/h). Antinuclear antibody was negative. The rheumatoid factor was positive at titers of 1:640. The C3 was low at 74 mg/dL (normal range, 88 to 177 mg/dL) and the C4 was 16 mg/dL (normal

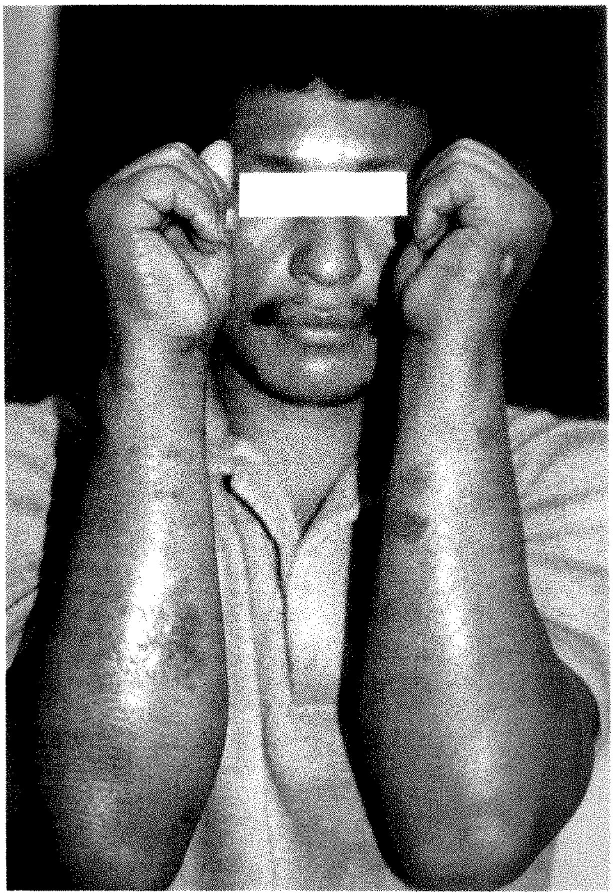

Fig 1. Patient demonstrating malar erythema and skin lesions of forearms and hands.

From the Department of Otolaryngology–Head and Neck Surgery, University of California, San Francisco (Lalwani, Tami), and the Hansen's Disease Research Program, Medical Research Institute of San Francisco (Gelber), San Francisco, California.

Presented at the meeting of the American Rhinologic Society, San Diego, California, September 8, 1990.

REPRINTS — Anil K. Lalwani, MD, Dept of Otolaryngology–Head and Neck Surgery, University of California, San Francisco, A730, 400 Parnassus, San Francisco, CA 94143.

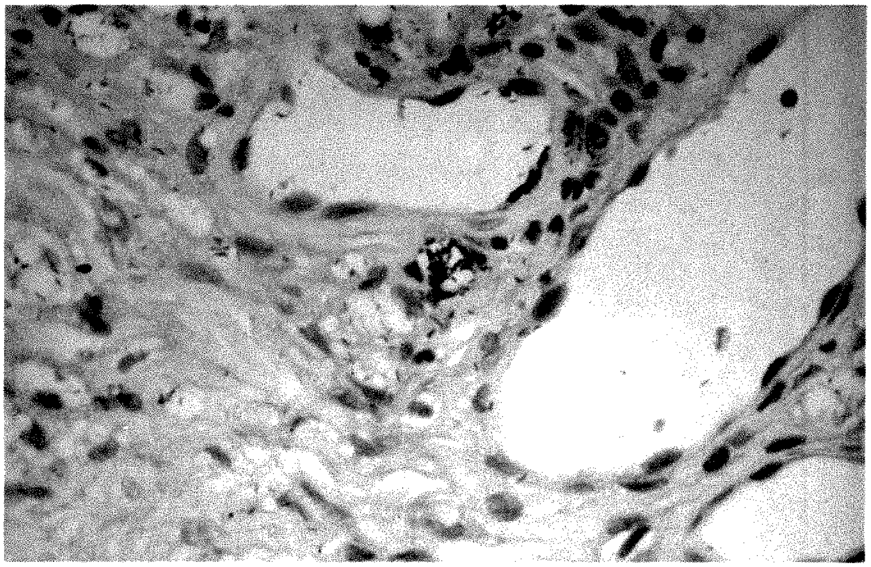

Fig 2. Acid-fast stain of earlobe biopsy specimen demonstrating numerous bacilli typical of lepromatous leprosy.

range, 15 to 45 mg/dL). Nasal septal and earlobe biopsies demonstrated abundant acid-fast bacilli with granuloma consistent with the diagnosis of LL (Fig 2). A 10-mm incisional biopsy of infiltrated skin of the right anterior thigh yielded 2.2 x 10^7 acid-fast bacilli. A homogenate of this biopsy grew *Mycobacterium leprae* convincingly in mice that was found sensitive to dapsone, rifampin, and clofazimine. This *M leprae* isolate was inhibited in mice fed 0.01% and 0.04% minocycline hydrochloride in diet (serum level, ≤ 0.17 μg/mL).

The patient was started on minocycline hydrochloride, 100 mg orally daily for 3 months, as part of a clinical research protocol. This was followed by standard combination therapy consisting of dapsone and rifampin. Within 1 week of the initiation of minocycline, nasal congestion and epistaxis resolved and skin lesions showed regression; furthermore, viability of *M leprae* obtained from sequential skin biopsies was reduced to 0% at 2 months and subsequently. Hypesthesia, however, persisted.

DISCUSSION

Leprosy is often referred to as "the oldest disease known to man."[2] The earliest written records date back to 600 BC in India, where it was called *kushta*. Around 190 BC, the Chinese attributed leprosy to overcrowding, promiscuity, absence of hygiene, and dirt. Two mummies found in a burial ground in El-Bigha (upper Egypt) and traced back to the sixth century AD provide the earliest reliable skeletal evidence of leprosy. Leprosy was probably brought to the West between 327 and 326 BC by the soldiers of Alexander the Great from the Indian campaign, and Johannes Damascenus (St John of Damascus [ca 675-749]) was the first Western author to associate the name "lepra" with the disease. In 1873, Hansen, in Bergen, Norway, reported that leprosy was not hereditary, but was an infectious disease caused by a bacillus.

Leprosy is caused by the acid-fast *M leprae* and, unlike *Mycobacterium tuberculosis*, is resistant to culturing on artificial media. *Mycobacterium leprae* has only been successfully grown in the cooler tissues of the foot pads of the mouse and the nine-banded armadillo (*Dasypus novemcinctus*). The generation time of *M leprae* in a mouse foot pad has been estimated to be 12.5 days, in contrast to only 24 hours required for *M tuberculosis*.[3] The estimated incubation time for leprosy is 3 to 10 years; it is the only bacterium that selectively invades peripheral nerves, causing irreversible cutaneous anesthesia and paralysis of muscles of the face and the extremities.

Clinically, leprosy presents a spectrum of diseases and has been classified into five groups based on clinical, histopathologic, and immunologic findings: tuberculoid, borderline-tuberculoid, borderline, borderline-lepromatous, and lepromatous.[3] These varied manifestations are a direct reflection of the vigor of the host's cell-mediated immune response to *M leprae* and provide a unique model for the study of immunoregulatory mechanisms in humans.[4] At one end of the spectrum, patients with tuberculoid leprosy are hyperergic to *M leprae*, have few skin lesions, and rarely have identifiable organisms on microscopy. At the other extreme, patients with LL are anergic to *M leprae* and have multiple skin lesions containing abundant bacilli. The patient presented here was judged to have LL because of extensive skin and peripheral nerve involvement, nasal manifestations, and histopathologic findings.

In contrast to the absence of nasal involvement seen with tuberculoid leprosy, nearly all patients with

LL have intranasal involvement early in the course of their disease, often occurring before manifestations of skin or nerve involvement.[5] Nasal symptoms often include obstruction, crusting, bleeding, and hyposmia. In one reported series of 77 patients, 94% reported nasal symptoms, 66% complained of obstruction, 74% had crust formation, and 52% reported bleeding.[6] Obstruction is usually secondary to granulomatous infiltration of nasal mucosa and crusting. Epistaxis is rarely severe, and blood-tinged discharge is more common. A 40% incidence of hyposmia has been reported. The degree of hyposmia is correlated with the extensiveness of lepromatous nasal involvement, sensory loss in the nose, and systemic manifestation.[7] Maxillary sinus mucosa — and less commonly, the mucosa of the other paranasal sinuses — can also be involved.[8] The pinna, hard and soft palate, epiglottis, and larynx are other common sites of involvement in the head and neck.

Early in the course of LL, examination of the nose is characterized by isolated nodules or plaques with pale, yellowish thickening of the nasal mucosa.[6] With progressive involvement there is generalized nodular infiltration of the mucosa with a predilection for the anterior inferior turbinate and the nasal septum. Septal perforation, saddle deformity, and atrophic rhinitis are late sequelae of this disease. Although nasal secretions harbor millions of live bacilli and are a common route of spread, viable bacilli can be eliminated within 1 week after treatment with rifampin or in several months with dapsone.

Positive rheumatoid factors (RFs) have been reported in 5% to 58% of patients.[9] Among the different types of leprosy, LL is more frequently associated with the presence of RFs than tuberculoid leprosy. Presence of RFs in these patients is associated with chronic, progressive arthritis primarily affecting the large joints. As in rheumatoid arthritis, the RFs react more strongly with rabbit than human IgG. The exact significance of RFs in leprosy remains speculative.

The standard therapeutic regimen for the treatment of leprosy consists of combination chemotherapy with dapsone and rifampin; clofazimine has also been used widely.[10] Although other therapeutic options used less frequently include ethionamide-prothionamide and streptomycin, the liver toxicity of ethionamide-prothionamide and the requirement to administer these agents parenterally sorely limit their use, especially in developing countries. Dapsone resistance is common, and daily treatment with rifampin is too expensive for most countries in which leprosy is prevalent. Clofazimine is associated with red-black skin pigmentation, and ethionamide therapy is frequently complicated by hepatotoxicity and gastrointestinal intolerance. Thus, the standard therapeutic regimen is limited by its cost and its side effects, and therefore a nontoxic therapeutic alternative is most welcome.

Minocycline, a tetracycline antibiotic, has been recently shown to be effective against *M leprae* infection in mice and humans.[10,11] The plasma minimal inhibitory concentration for *M leprae* was <0.2 μg/mL, and the plasma level obtained with a standard adult dose of 100 mg of minocycline administered twice daily is 2 to 4 μg/mL, which is significantly above the minimal inhibitory concentration. In comparison to the other antileprosy drugs, minocycline had greater bactericidal activity than each except rifampin, and was additive when combined with dapsone, kanamycin sulfate, and rifampin. In addition, minocycline has been used chronically in patients, especially in treatment of acne vulgaris, for over two decades and has been found to be relatively safe. Minocycline clinical trials in the treatment of leprosy are in progress; as demonstrated by the response in our patient, this antibiotic shows great promise. In the future, minocycline may either supplement or replace the current standard therapy for the treatment of leprosy.

In summary, while infrequent in the United States, leprosy is a common disease in many parts of the world. In LL, nasal involvement occurs early and almost universally. Typically, the patient complains of nasal obstruction, crusting, bleeding, and hyposmia. Although nasal discharge, which harbors millions of bacilli, is a common route of spread, treatment reduces the acid-fast bacillus count to zero within weeks. Prompt treatment prevents late secondary cosmetic deformities. Recently, minocycline has been shown to be promising as an effective and relatively safe chemotherapeutic agent in the treatment of leprosy. The case presented typifies the excellent clinical response documented in the ongoing clinical trial of minocycline. Leprosy should be included in the differential diagnosis for patients with chronic nasal symptoms so that the potential morbidity that occasionally accompanies this disease can be avoided.

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MAURICE H. COTTLE HONOR AWARD

The American Rhinologic Society wishes to announce the competition for the Maurice H. Cottle Honor Award. The manuscript submitted should represent basic or clinical rhinologic research. The winner of the competition will receive a check for $1,000 and will be requested to present the winning manuscript at the 38th annual scientific meeting, which will be held on Saturday, September 12, 1992, in Washington, DC. Please submit manuscript by June 1, 1992, to Dr George Facer, Secretary, American Rhinologic Society, 200 First Street SW, Rochester, MN 55905.

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PERICHONDRIAL MICROVASCULAR FREE TRANSFER: CREATION OF A COMPOUND FLAP FOR LARYNGEAL RECONSTRUCTION IN RABBITS

PIERRE R. DELAERE, MD
WILLY D. BOECKX, MD, PHD
BOUWDEWIJN VANDAMME, MD, PHD
PAUL J. GUELINCKX, MD, PHD
FRANS OSTYN, MD
LEUVEN, BELGIUM

A free revascularized compound perichondrial flap was used over an intralaryngeally placed stent for reconstruction of a frontal laryngeal defect. The microvascular flap replaced the cartilaginous and mucosal defect. Short-term results showed successful reconstruction with a patent airway and viable mucosa. The vascularized sheet of perichondrium was not chosen for its neochondrogenetic effect, but it served as a vascular bed, nourishing the mucous and cartilaginous components in the compound flap. It is suggested that for clinical purposes the reliable fascia forearm flap, which is available in large amounts, can be used as a transferable vascularized bed with a thickness comparable to that of the perichondrial flap.

KEY WORDS — laryngotracheal surgery, microvascular flap, perichondrium, reconstruction.

INTRODUCTION

Several specific conditions must be fulfilled to ensure successful results in laryngotracheal reconstruction. For the reestablishment of the airway, reconstruction techniques require restoration of a mucosal component and a cartilaginous component.[1] Clinically applicable techniques need to be well vascularized and one-stage. A mucosal layer, however, is not an essential prerequisite in the reconstruction of a full-thickness laryngeal wall defect. Some reports clearly demonstrate that respiratory mucosal migration is possible over a well-vascularized fascial, perichondrial, or periosteal layer.[2]

Many techniques have been proposed for laryngotracheal reconstruction.[3-10] Only a few of them respond to the requirements of internal lining, support, and vascularization. The epithelialized microvascular iliac crest flap[9] and the preformed auricular cartilage composite graft[10] fulfill the basic requirements, but are two-stage procedures. The other proposed regional flaps are poorly nourished through small muscle insertions or have unfavorable surfaces for receiving a mucosal layer. At the moment, there are no reliable reconstruction methods available for large tracheal defects. For laryngeal reconstruction, the epiglottis can be used as an advancement flap for repair of a frontal laryngeal thyroid defect.[11] This is an effective and relatively simple one-stage surgical approach with good functional results.[12,13]

Because of the different problems met in laryngotracheal tissue repair, it is preferable to perform an end-to-end reanastomosis if feasible in cases of supraglottic laryngectomy and tracheal resection (with a maximum of 5 cm) to restore the continuity of the respiratory tract.

In recent years, microvascular surgery has revolutionized reconstruction in most areas of surgery. However, it is remarkable that only one account of laryngotracheal reconstruction using a revascularized microvascular flap is found in the literature. Kambič et al[9] reported in 1986 the idea of resolving a subglottic laryngeal stenosis with an epithelialized microvascular iliac crest flap. They obtained a good result in one patient after a follow-up period of 6 months. As mentioned above, it is a two-stage procedure, and the reliability of a piece of bone used to restore a laryngeal or tracheal wall defect can be questioned. Rigid bone grafts cannot conform to the contour of a laryngotracheal defect with a tight seal.

The clinical value of a reliable reconstruction technique is evident: functional repair of the upper respiratory system after tumor resection, trauma, or removal of stenotic segments. With the requirements of lining, vascularization, and support in mind, we created a one-stage reconstruction method with hopeful short-term experimental results. The keystone of the technique is a thin, pliable revascularized sheet of auricular perichondrium that is available in large amounts in the rabbit. The well-vascularized perichondrium can be turned over 180° with preservation of its distal vascularization, providing a vascular bed for the cartilage graft, for reconstruction of thyroid cartilage mucosa and an anterior cricoid defect. The internal distal layer of the

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From the Department of Otorhinolaryngology (Delaere, Ostyn), the Division of Plastic and Reconstructive Surgery (Boeckx, Guelinckx), and the Department of Pathologic Anatomy (Vandamme), University Hospital St Rafaël, Leuven, Belgium.

REPRINTS — Pierre R. Delaere, MD, Microsurgery Research Center, University Hospital St Rafaël, KU Leuven, Kapucijnenvoer 31, B-3000 Leuven, Belgium.

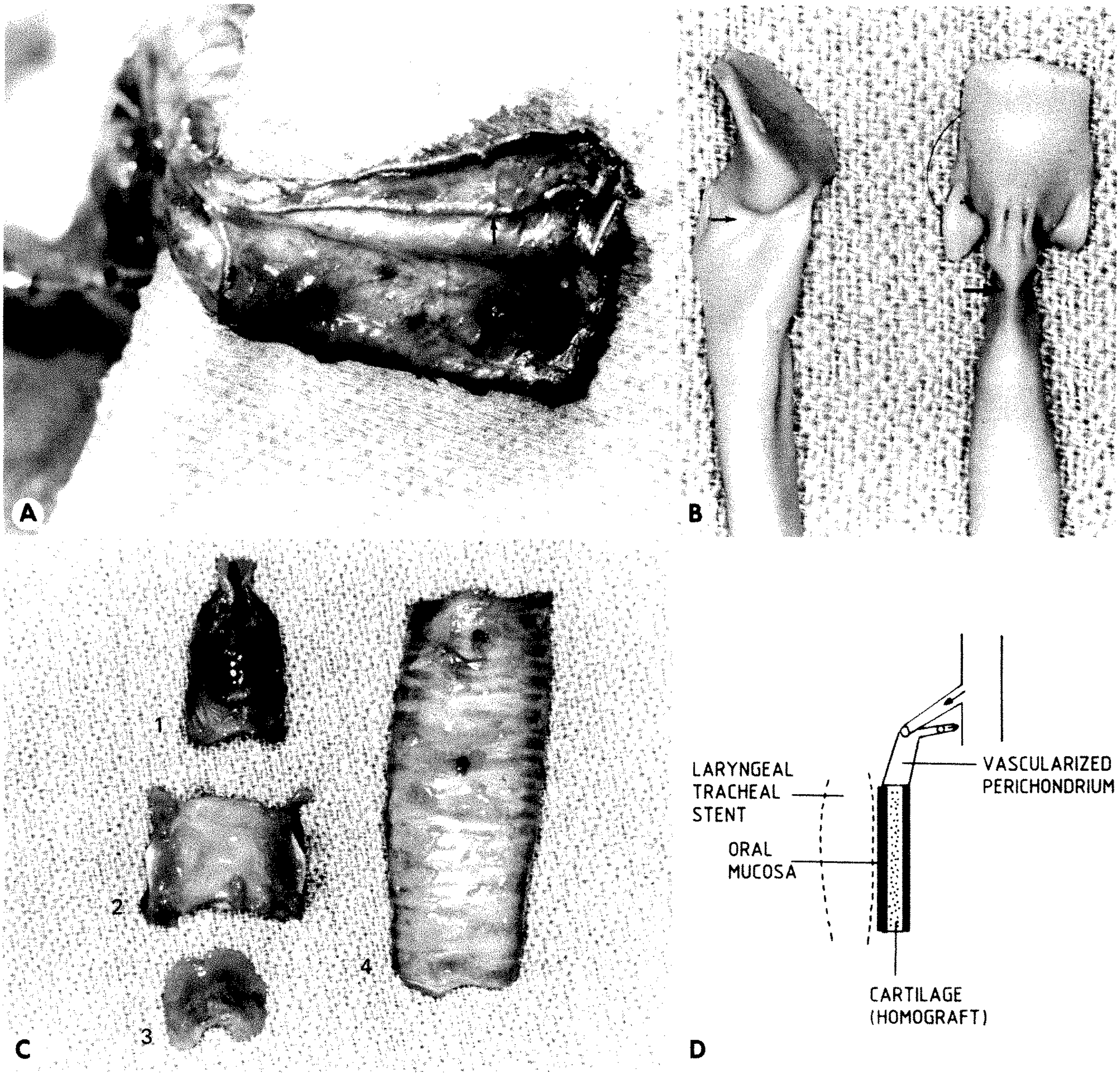


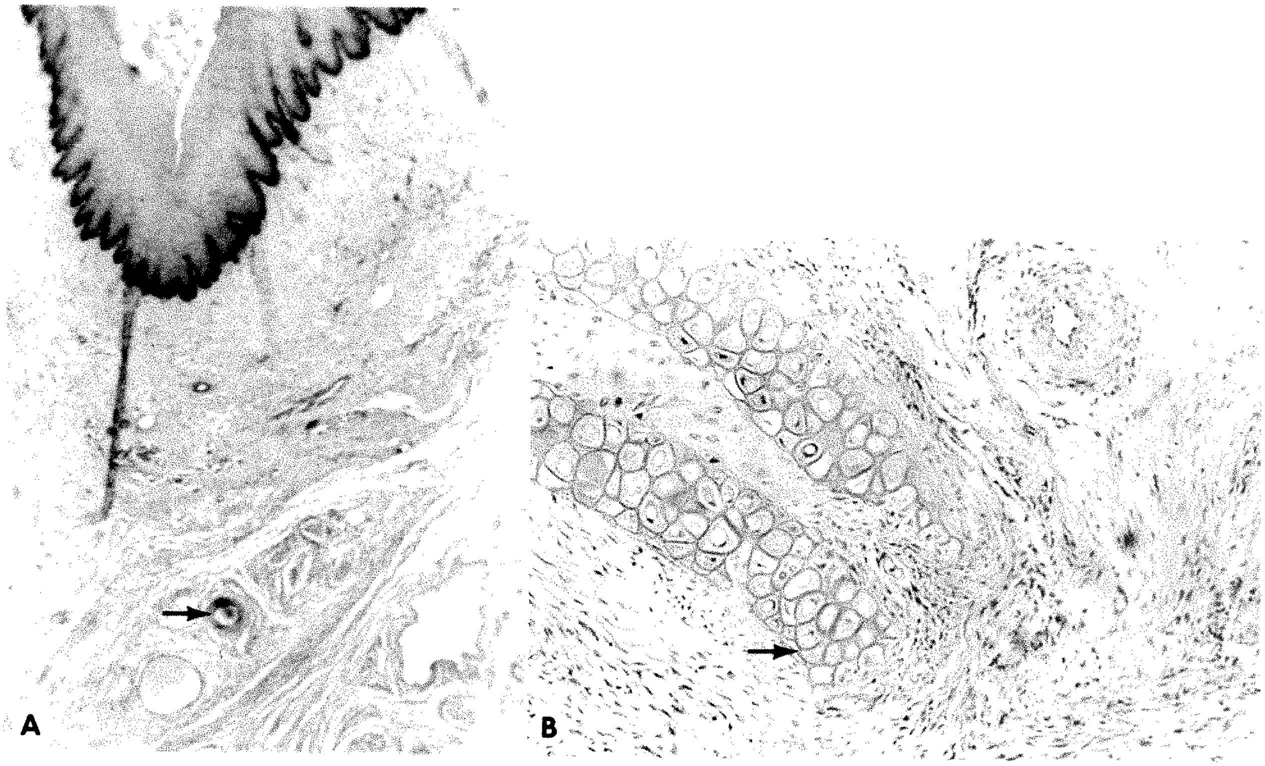
Fig 1. Operative procedure. A) Perichondrial flap with proximal vascular pedicle. Large arrow — central auricular artery, small arrow — central auricular vein. B) Intralaryngeal silicone stent over which reconstruction was performed with anterior commissure (large arrow) and impression of arytenoid cartilage (small arrow). C) Freshly preserved laryngotracheal cartilage. Only thyroid cartilage homograft was used. 1 — cricoid cartilage, 2 — thyroid cartilage, 3 — epiglottis, 4 — tracheal cartilage. D) Principle of reconstruction: revascularized perichondrial flap grafted on its outer surface with full-thickness oral mucosa graft. Homogenous cartilage graft is protected within vascular bed of perichondrium.

perichondrial graft can receive a mucosal graft or can be used as viable framework over which reepithelialization can occur from the marginal epithelium surrounding the defect when no mucosal layer is provided.

MATERIAL AND METHODS

Ten New Zealand white rabbits weighing 2 to 2.5 kg were operated on. A compound perichondrial flap[14] from the right ear was transplanted to the neck and sutured to the neck vessels for revascularization after insertion in the laryngeal defect.

Operative Procedure. Inhalation anesthesia in a half-open system was used after intramuscular induction of anesthesia. The induction was with Hypnorm (Duphar, Belgium) administered intramuscularly at 0.4 mg/kg body weight. Five minutes after induction, a mixture of oxygen and nitrous oxide was given through a mask. The perichondrial graft was harvested from the right ear after elevation of the skin. A 4 x 10-cm piece was elevated on its vascular pedicle, consisting of the central auricular artery (0.75 to 1.0 mm external diameter) and vein (1.0 to 1.25 mm external diameter; Fig 1A). Before laryngeal resection, an endotracheal intubation was performed through a tracheotomy incision. The thyroid cartilage with mucosa and both vocal cords



were removed. A piece of full-thickness oral mucosa, measuring 2 x 2 cm, was taken from the buccal region and sutured over the silicone laryngeal stent (Fig 1B) to the laryngeal mucosal remnants. Interrupted 8-0 nylon sutures were used with the knots lying outside the lumen. With the same suture material, the perichondrium was stitched to the submucosa of the oral graft so as to provide a vascular bed for the free mucosal graft. An extra, centrally placed stitch gave a better contact between the free graft and the perichondrium. The distal end of the perichondrial graft was sutured to the right side of the mucosal graft. A freshly preserved thyroid cartilage homograft (Fig 1C) was brought over this second layer and attached with 8-0 nylon sutures. The perichondrial flap was turned over 180° at the left side of the transplanted cartilage and fixed to the thyroid homograft. Revascularization took place by an end-to-side arterial anastomosis with the right common carotid artery and an end-to-end venous anastomosis with the right external jugular vein (11-0 nylon; Fig 1D).

The free oral mucosal graft was well supported internally by the stent, which was fabricated from an impression of the normal rabbit laryngeal lumen. In this way there was a tight contact with the vascularized perichondrium graft bed, which made the necessity for a two-step procedure obviated.

The treatment and care of the rabbits were according to the rules of the American Physiological Society. Ambi-pen (penicillin G suspension, 30,000 U/100 mg) was administered for prophylaxis. The laryngeal stent was removed after 3 weeks. During anesthesia the tracheotomy opening was closed and the patency of the laryngeal lumen was assessed by clinical evaluation of respiratory function. One hour after tracheotomy closure, methylene blue was injected in the central auricular artery. After injection, the rabbits were painlessly killed for histologic evaluation of the reconstruction site. All biopsy specimens were processed according to the classic hematoxylin and eosin staining technique.

RESULTS

One animal had an infection of the neck wound with vascular thrombosis of the vascular pedicle. It was not clear if a primary thrombosis or a primary infection with subsequent thrombosis was the reason for reconstruction failure.

The other animals displayed a normal breathing pattern clinically without signs of stridor after removal of the laryngeal stent and closure of the tracheotomy. In 9 of the 10 rabbits there was a patent vascular anastomosis after 3 weeks. A blue discoloration of the whole perichondrial length was seen after intraarterial methylene blue injection, which proved the viability of the flap even at its distal end. There was a close color match between the mucosa of the reconstructed part and the surrounding normal laryngeal mucosa on postmortem macroscopic examination.

The epithelium of the reconstructed laryngeal mucosa consisted of nonciliated squamous cells (Fig 2A). The oral mucosa graft took successfully on its revascularized perichondrium bed. The homogenous cartilage grafts were well preserved in all cases, with a viable appearance of the chondrocytes within the lacunae. The chondrogenetic capacity of the vascularized perichondrium after 3 weeks was in accordance with the findings by Donski and O'Brien[15]: formation of a cartilage plate with mature cartilage cells (Fig 2B).

DISCUSSION

The short-term results of the chondral-reinforced perichondrial flap point out that the reconstruction technique offers a reliable tool for experimental laryngeal reconstruction. With this technique, the wall of a full-thickness laryngeal defect is replaced by four layers. The free mucosal and cartilage grafts are nourished through a thin, pliable and continuous revascularized sheet of tissue. The perichondrial layer provides a bed for survival of the free mucosal graft. The disadvantage of this experimental technique is the need for a laryngeal stent to assure a good internal support keeping the mucosal graft in close contact against its vascular bed. Use of a laryngeal stent in clinical cases gives some problems, and it is expected that the chance for successful reconstruction is enhanced without the use of stents. We fully agree with Peacock and Van Winkle,[16] who stated that there is no question that a laryngotracheal stent is deleterious to the basic mechanisms of wound healing. The same reconstruction is possible without the use of a laryngeal stent if no mucosal graft is provided. In these circumstances, a spontaneous reepithelialization over the perichondrial layer is looked for. There are, however, no quantitative data available indicating over how large an area reepithelialization is possible without provoking granulation and fibrous tissue formation. A cartilaginous framework defect is best replaced by cartilage. In this experimental study, the homogenous thyroid cartilage graft provides the necessary support to the airway. Autogenous cartilage grafts are preferable, but not always available for reconstruction of larger defects.

Autogenous rib cartilage is the ideal source if a small amount of cartilage is needed, as for lumen augmentation to resolve cricoid stenosis. In cases in which greater areas of rigid support have to be reconstructed, the use of freshly preserved homogenous thyroid cartilage can be a good alternative. Cartilage homografts have an immunologic privilege, because they can be transplanted without provoking an immune response.[17] As pointed out by Curran and Gibson in 1956,[18] freshly preserved cartilage retains some metabolic activity for at least 6 weeks when stored at 4°C and regains a part of its original metabolic activity after transplantation. A vascularized perichondrium flap wrapped around the cartilage graft can be seen as a protective vascular bed, isolating the graft from the surrounding tissues.

The clinical equivalent of the experimental perichondrial flap is the free revascularized fascia flap. The physical characteristics of perichondrium and fascia flaps are completely comparable except for the neochondrogenetic effect typical of perichondrium grafts. The value of a vascularized fascia flap has been emphasized by different authors.[19,20]

A fascia flap can be harvested with minimal or no donor site defect and brings some vascularity to areas lacking a blood supply because of irradiation and scarring. The excellent pliability and vascularization could be very useful in laryngotracheal reconstruction. Among the fascia flaps, the radial artery fascia free flap is the most useful because of the great amount of tissue that is available and because of its long pedicle containing vessels of a diameter that makes revascularization easy.[21]

CONCLUSION

The compound revascularized perichondrial flap lends itself particularly well to the theoretic requirements of laryngeal reconstruction. This experimental study has proven the capability of the perichondrial flap in receiving a mucosal graft and in protecting a cartilage homograft within a vascular bed. Further long-term examination continues to assess spontaneous reepithelialization over perichondrial flaps and the possibility of circumferential use of the flap in tracheal reconstruction.

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EXPERIMENTAL BLUNT INJURY TO THE LARYNX

SHIANN YANN LEE, MD, FICS
TAIPEI, TAIWAN, REPUBLIC OF CHINA

This article deals with the fracture line distribution and severity of laryngeal trauma. Laryngeal trauma was experimentally inflicted on 100 human laryngeal specimens with the impact of a 2.0-kg weight falling by gravity from a height of 100 cm. According to the previous pilot experiment and clinical experiences, the author classified the severity of fracture into four grades. The results showed no significant sex difference in the severity of fracture with reference to age distribution, especially severe injury in older age groups. The pattern of fracture lines of the laryngeal cartilage was observed and traced in four selected locations, including the thyroid notch, central zone of the thyroid cartilage, cricothyroid region, and cricoid. The distributions of fracture lines are illustrated. The experiment is described in detail.

KEY WORDS — blunt injury, experimental trauma, human larynx.

INTRODUCTION

Trauma of the larynx due to anterior neck injury has become an important problem for the otolaryngologist because of the increasing incidence and severity of traffic accidents.[1] Besides, a wide variety of mishaps may cause external laryngeal injuries: gunshot and stab wounds and strangulation in combat,[2] sports trauma,[3-5] and sharp or blunt anterior neck injuries in industrial fields.[6] Many articles have clearly elucidated the causes and symptoms over the past decades.[7-9] But so far, it seems to this author, a recognized format for the management of acute laryngotracheal injuries and chronic stenosis has not been established.

The endolaryngeal space relies on the integrity of the laryngeal cartilaginous structure. Thus, when fracture of the cartilages has occurred, the lumen will become narrowed, stenosed, and deformed in the course of time. Therefore, early definitive diagnosis is important, and adequate management including open reduction of the fractured cartilages is mandatory in certain cases.[10,11]

The purpose of this paper is to observe the pattern of fracture lines on the laryngeal cartilage induced by experimental external blunt trauma in 100 human laryngeal specimens. It was expected that these experimental data would provide important information on the nature of the fracture lines and possible clinical symptoms or findings, which would consequently lead to better estimation of the lesion and surgical treatment.[12]

MATERIALS AND METHODS

One hundred larynges from patients who died of conditions unrelated to the larynx were obtained. Each specimen consisted of the larynx with four tracheal rings attached to it and was taken at autopsy from 50 males and 50 females. All the soft tissues around the laryngeal framework were removed, except the thyroid gland and strap muscles. The specimens were preserved in 10% formalin solution for about 2 years before the present experiment. Specimens were selected only if there were no gross anatomic abnormalities, with the exception of two cases in which tracheostomy had been performed at the level of the third to fourth tracheal rings. The age of the patients ranged from 2 to 83 years in males and from 4 to 81 years in females.

An experiment "scaffold" (Fig 1) was established to provide an impact upon the anterior surface of

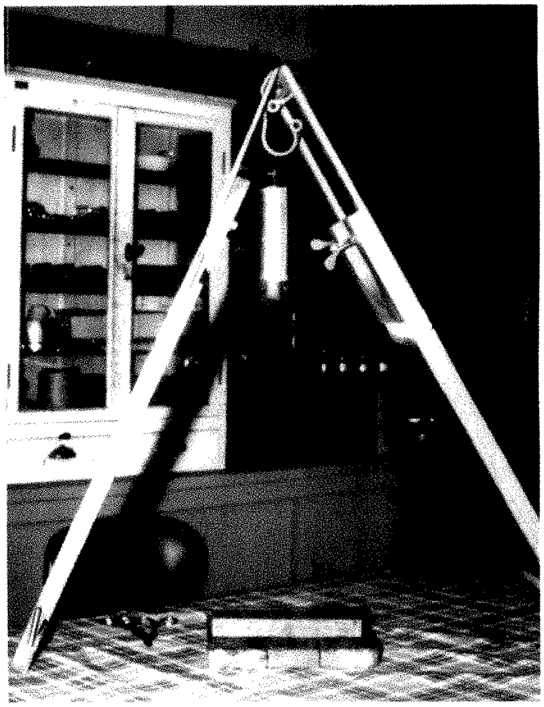

Fig 1. Experimental scaffold for blunt impact on human larynx. Bent lead pipe 2.0 kg in weight with blunt head 2 x 2 cm in size was hung 100 cm above specimen, which was fixed on wooden board.

From the Department of Otolaryngology, National Taiwan University Hospital, Taipei, Taiwan, Republic of China. This research was supported by the National Science Council, Republic of China (NSC79-0412-B002-122).

REPRINTS — Shiann Yann Lee, MD, FICS, Dept of Otolaryngology, National Taiwan University Hospital, 1 Chang-Te St, Taipei, Taiwan, Republic of China.

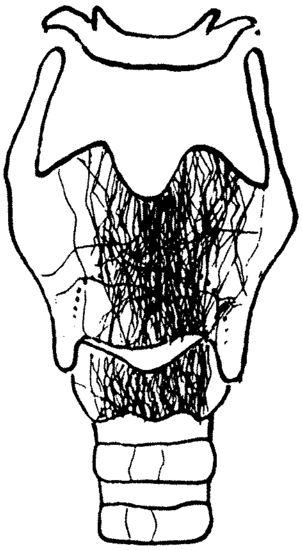

Fig 2. All fracture lines composed and put together (n = 100).

the specimen. A blunt impact was generated with a 2.0-kg weight falling from a 100-cm distance. A pilot study revealed that this impact was the minimal tolerance of the laryngeal cartilage to developing fracture lines.[13] Therefore, 2.0 kg was chosen. The author assumed the experimental impact was comparable to the force elicited when the larynx hits an object at a velocity of 50 km/h, provided that the larynx weighs 0.2 kg. A bent lead pipe 2.0 kg in weight with a blunt head 2 x 2 cm in size was hung 100 cm straight above the specimen, which was put with the anterior surface up and bandaged and fixed on a wooden board.

The specimens were impacted in the anteroposterior direction by the free-fall gravity of the lead pipe to induce experimental collision. Each specimen was given a single impact. Impact was inflicted on four regions: at the level of the thyroid notch, on the middle portion of the thyroid cartilage, on the cricothyroid membrane, and on the cricoid. Four regions were marked with india ink on the bandage. After the single impact, each larynx was dissected and the remaining soft tissues around the larynx were removed except for the perichondrium. The hyoid bone, thyroid cartilage, cricoid cartilage, and tracheal rings were exposed to examine the fracture line or laceration of the perichondrium.

According to the pilot study and clinical experience, the severity of fracture was classified into four grades as follows: grade 0, no fracture; grade 1, single or multiple fractures on one cartilage without laceration of the perichondrium; grade 2, single or multiple fractures on one cartilage with laceration of the perichondrium, or fractures on two cartilages; and grade 3, fragmentation of one or two cartilages, penetrating injury, or collapse of the entire laryngeal structure. The characteristic patterns of fracture differed with the location of the impact.

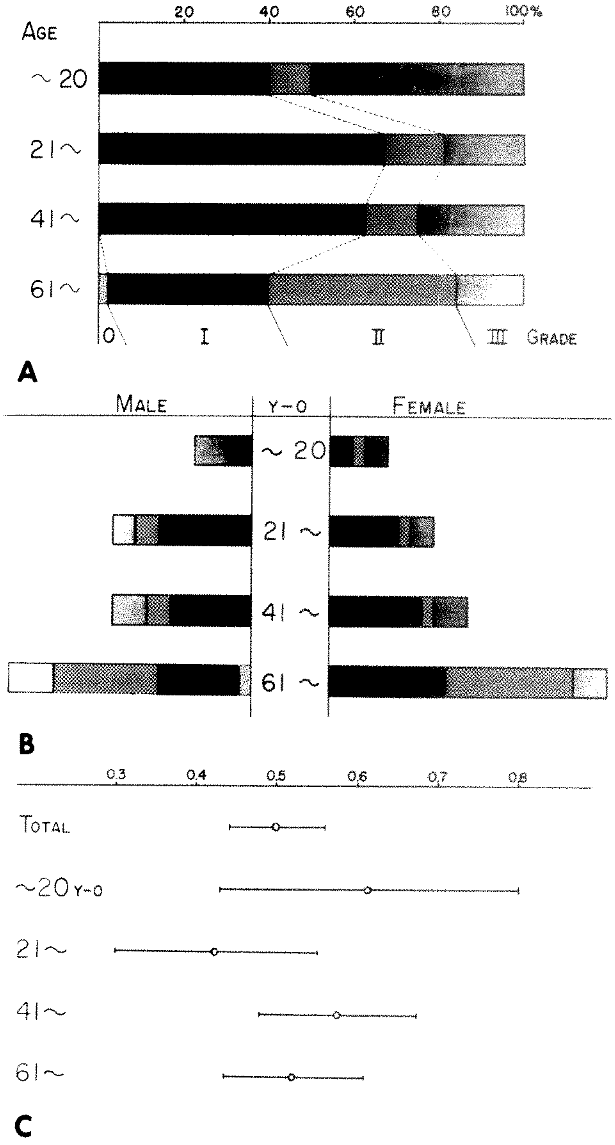

Fig 3. Fracture severity (n = 100 cases). A) Percentile distribution in each age group. B) Distribution in each age group and both sexes. C) Age distribution (Ridit [relative to an identified distribution] analysis).

All fracture lines in each type of impact were superposed together in a schematic drawing, shown in Fig 2.

RESULTS

In this series of experimental laryngeal trauma in 50 males and 50 females, there was no evident sex difference in the severity of fracture with reference to age distribution (Fig 3A). Therefore, both sexes were grouped together for further observation (Fig 3B). Severe injuries (grades 2 and 3) occurred in the young (under 20 years) and old (over 61 years) age groups. Mild fracture developed in the middle age groups more frequently. There were 50 cases with grade 1 fracture, the distribution of which was rather homogeneous among age groups (Fig 3C).

When a force was applied in 31 cases to the thy-

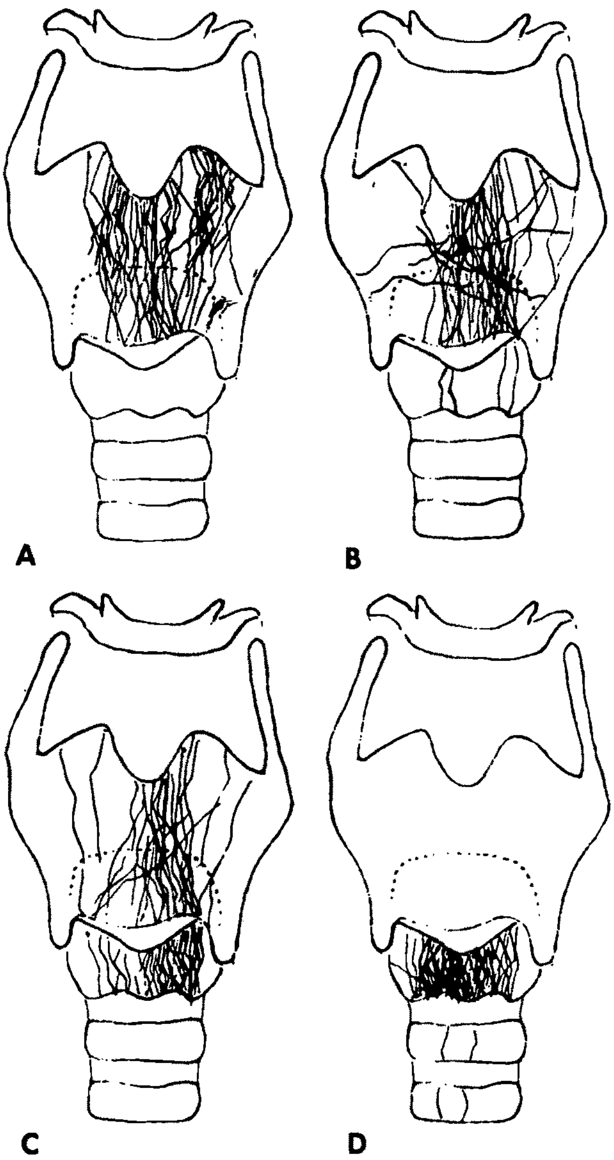

Fig 4. Fracture line distribution. A) When impact was applied to upper thyroid cartilage ($n = 31$). B) When impact was applied to middle portion of thyroid cartilage ($n = 27$). C) When impact was applied to cricothyroid region ($n = 20$). D) When impact was applied to cricoid ($n = 22$).

roid notch or upper portion of the thyroid cartilage (Fig 4A), the fracture lines scattered over the paramedian area of the bilateral lamina and condensed on the upper border of the thyroid cartilage. The fracture lines all appeared in the longitudinal direction. With impacts in 27 cases on the middle portion of the thyroid cartilage at the glottic level (Fig 4B), the fracture lines concentrated in the central zone of this cartilage and involved the thyroid notch. During the dissection of the specimen, overlapping of fractured thyroid alae was noted in some cases. The fracture lines appeared in vertical, oblique, and horizontal directions, crossing over the lamina. When the impact was aimed at the cricothyroid membrane in 20 cases, the force was inevitably exerted on both the thyroid and cricoid cartilages. Thus, fracture lines often extended to both cartilages. The fracture lines centered around the median part of the thyroid cartilage and the anterior portion of the cricoid (Fig 4C). Also, laceration of the cricothyroid membrane was frequently noted. When the weight directly hit the cricoid cartilage in 22 cases (Fig 4D), the injury could reach the tracheal rings, but most of the fracture lines were scattered diffusely over the cricoid arch. The fragmentation of the cricoid cartilage was also noted in some cases.

The patterns of all fracture lines were combined as shown in Fig 2 to reveal a trauma concentration over the central third of the thyroid and cricoid cartilages.

DISCUSSION

In this study, the force (F) was estimated as $F = mgh$ (law of free fall), where $m = 2.0$ kg and $h = 100$ cm. (The symbol g stands for the acceleration of gravity.) The experimental setting can be assumed as comparable to the condition of a hypothetic traffic accident when the larynx is moving with a constant velocity (V) and hits a wall. Since the average weight of the laryngeal specimen was about 0.2 kg (M), V was calculated as 50.4 km/h, according to the equation $1/2\,(M)V^2 = mgh$.

The specimen was so prepared as to simulate clinical conditions as exactly as possible. The bandage can be comparable to the neck skin and soft tissue layers. Another purpose of the bandage was to prevent sharp injury but produce a blunt collision. The wooden board was used to represent the cervical vertebrae, and fixation was to keep the specimen in place just as in the anterior neck.

Because the specimens were preserved in 10% formalin solution for more than 2 years, the cartilage might have become more fragile and less elastic than in the fresh specimen. Therefore, it must be taken into consideration that the laryngeal tolerance was somewhat decreased in this experiment.

In the experiment, there were four impact location groups. The cricothyroid membrane and cricoid cartilage were viewed as two independent sites. Clinically, however, each of the two sites is too small to be separated in blunt trauma. In fact, pure cricothyroid membrane laceration or single cricoid fracture is quite unusual, and the latter is often accompanied by fracture of the thyroid cartilage or collapse of the tracheal rings. But in this study, a localized impact upon the cricoid cartilage was applied and it was found that only one case developed fracture of the tracheal rings in addition to cricoid fracture. Since the site of the impact was too localized, it was not particularly related to the grading of severity.

As for changes of the larynx with age, mineralization of the thyroid cartilage was reported to begin after the age of 18 in both sexes.[14,15] It starts in the lower horn and progresses cranially along the posterior border and anteriorly. In the normal population, 50% have complete ossification or calcification of the thyroid notch after middle age. No significant sex difference has been found in the mineralization pattern of the cricoid cartilage, and ossification or calcification spreads from the body of the cartilage, although calcium deposition may be absent even in the oldest patient. In this experiment, the fracture lines were confined almost to the anterior one third of the thyroid cartilage and the anterior portion of the cricoid. It appeared that the distribution of the fractures corresponded to the physiologic extent of ossification or calcification of the laryngeal cartilages. The high incidence of severe fracture (grades 2 and 3) was noted in the oldest age groups, especially over 61 years. Thus, the physiologic mineralization of the cartilage seemed to play an important role in laryngeal trauma. These experimental results showed that grade 3 fracture also occurred in the young age groups (under 20 years), and the majority of the cases developed entire laryngeal collapse. The reason might be that the young larynges were so fine and small that they could not tolerate the impact weight. Clinically, laryngeal trauma is rare in young age groups, but it will be a fatal situation should it occur as observed in this experimental condition.

Generally, by the "hammer and anvil" or "peeling" effect, laceration of the perichondrium develops. The mucosa and perichondrium are crushed, torn, or stripped. Bleeding and hematoma formation then ensue. Laceration of the perichondrium may induce perichondritis and even cartilage necrosis. The soft tissue may be exposed into the laryngeal lumen, and subsequent proliferation of granulation and fibrous tissue may occupy the laryngeal space several weeks later. The patient will lose his or her respiratory tract and phonatory function, or keep a permanent tracheostoma with decannulation difficulty. In this experiment, dissection and observation of the fractured thyroid cartilage revealed that laceration of the perichondrium on the anterior surface frequently combined with overlapping of the cartilage. Occasionally, the mucosa was not torn and the endotracheal space was still patent. However, if fracture of the thyroid cartilage was accompanied by fragmentation of the cricoid cartilage, deformity of the laryngeal contour and displacement of the laryngeal box were almost always noted and angulation of the airway was found at the cricothyroid junction together with a tear in the subglottic mucosa. Therefore, this type of injury should be considered critical.

On the basis of the results of this experimental study of laryngeal trauma, it appears that most damage is inflicted on the middle third of the anterior thyroid cartilage and cricoid arch. The luminal narrowing of the airway in the cricothyroid region is commonly due to collapse of the anterior wall, which will be found with much more severe pathologic change. The cartilage defect may be noted over this part in chronic cases. The present experimental study of 100 human larynges will contribute much information in the treatment of laryngotracheal stenosis caused by blunt external neck injury.

SUMMARY

Experimental trauma was inflicted on 100 laryngeal specimens taken from 50 male and 50 female cadavers. A blunt impact was generated with a 2.0-kg weight falling from a 100-cm height downward. The experimental results showed that there was no definite sex difference in the severity of laryngeal fracture. Fracture lines were observed and traced. They were distributed and concentrated over the middle third of the thyroid cartilage and the anterior portion of the cricoid arch. Cricothyroid fracture is considered to be a critical injury. Clinically, open reduction by exploration of the stenotic laryngotracheal structure is mandatory.

In reconstructive surgery, it should be considered that the majority of tissue damage is distributed over the anterior wall of the laryngotrachea.

ACKNOWLEDGMENTS — I express appreciation to Professor Shuji Sawaki (Department of Otolaryngology, Yokohama City University, Japan), Professor Yoshiyuki Yoshimura (Department of Pathology, Yokohama City University, Japan), Professor Hajime Hirose (Research Institute of Logopedics and Phoniatrics, Faculty of Medicine, University of Tokyo, Japan), and Professor Mow Ming Hsu (Department of Otolaryngology, National Taiwan University Hospital) for their kind suggestions and encouragement throughout this study. I thank Sheng-Hwa Chang for her technical assistance in preparation of the manuscript and One-Che Linne, MD (Chairman, Department of Otolaryngology, Taipei Municipal Jenai Hospital), who read the manuscript before presentation.

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INTERNATIONAL HEARING AID CONFERENCE
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An International Hearing Aid Conference will be held June 15-17, 1993, at The University of Iowa, Iowa City. For information on registration and accommodation, contact the Conference Center, University of Iowa, Memorial Union, Iowa City, IA 52242; (319) 335-3231, Fax (319) 335-3407. For information on Call for Papers, contact Regina Tisor (319) 356-2471, Fax (319) 356-4547. We have applied for Continuing Education Units from ASHA and HAIC.

Ann Otol Rhinol Laryngol 101:1992

IMAGING CASE STUDY OF THE MONTH

THREE-DIMENSIONAL COMPUTED TOMOGRAPHY IN A CASE OF CRANIOFACIAL FIBROUS DYSPLASIA

EDWARD J. RICCIARDELLI, MD
JAMES A. BORROW, MD
KATHLEEN H. MAKIELSKI, MD
SEATTLE, WASHINGTON

Multiplanar reformatted computed tomography (MPR-CT) has proven useful in providing global anatomic reconstructions of complex craniofacial disorders. Head and neck surgeons have documented the role of three-dimensional (3-D) CT in selected cases of craniofacial trauma, neoplastic disease, and congenital disorders.

We present a case of craniofacial fibrous dysplasia involving the maxillary, sphenoidal, frontal, and zygomatic bones imaged by conventional and MPR-CT radiographs. The 3-D image provided valuable information to the surgeon and patient during the preoperative counseling period in discussing surgical options. The images also proved useful in-

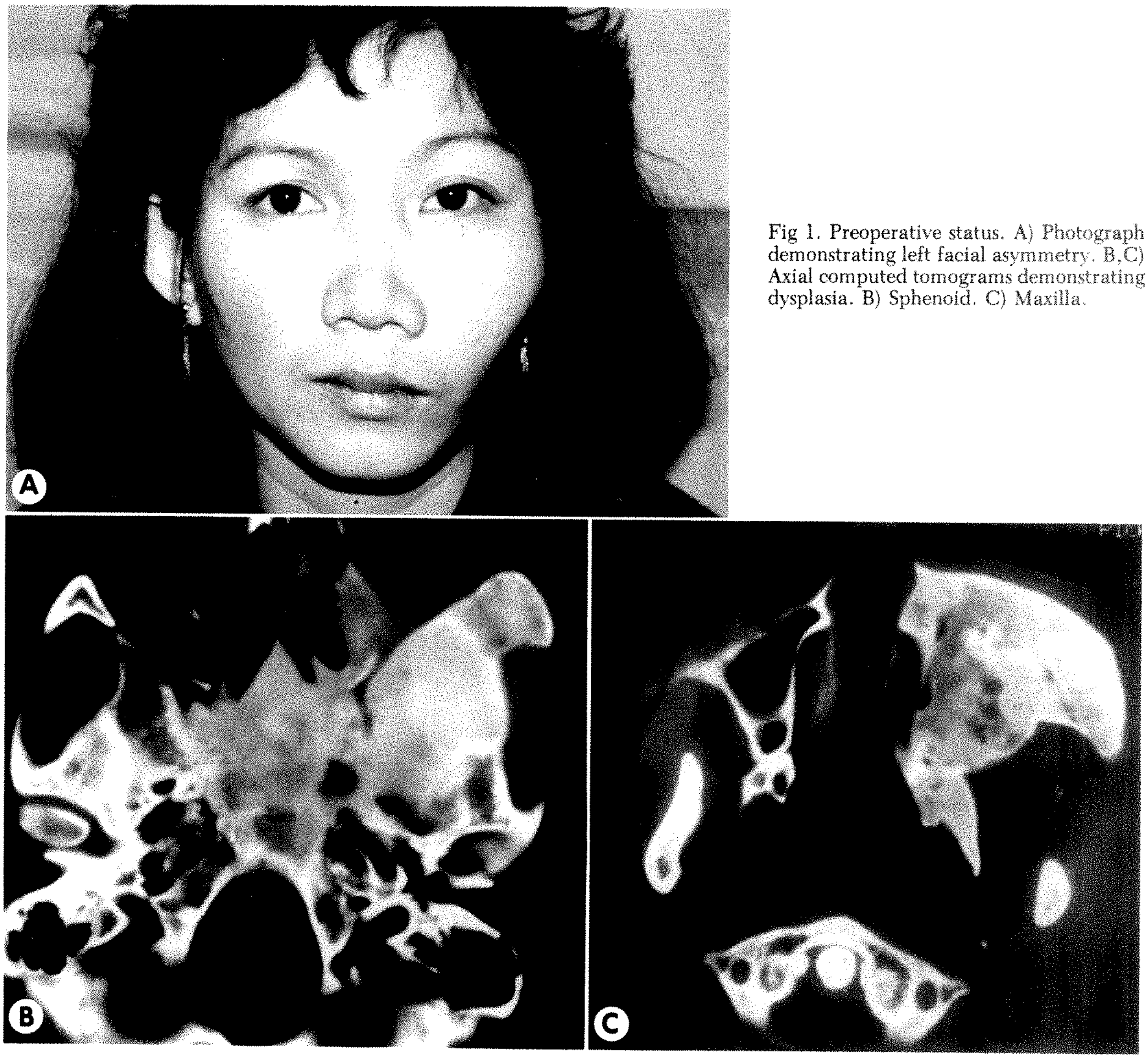

Fig 1. Preoperative status. A) Photograph demonstrating left facial asymmetry. B,C) Axial computed tomograms demonstrating dysplasia. B) Sphenoid. C) Maxilla.

From the Department of Otolaryngology–Head and Neck Surgery, University of Washington, Seattle, Washington (Ricciardelli, Makielski).

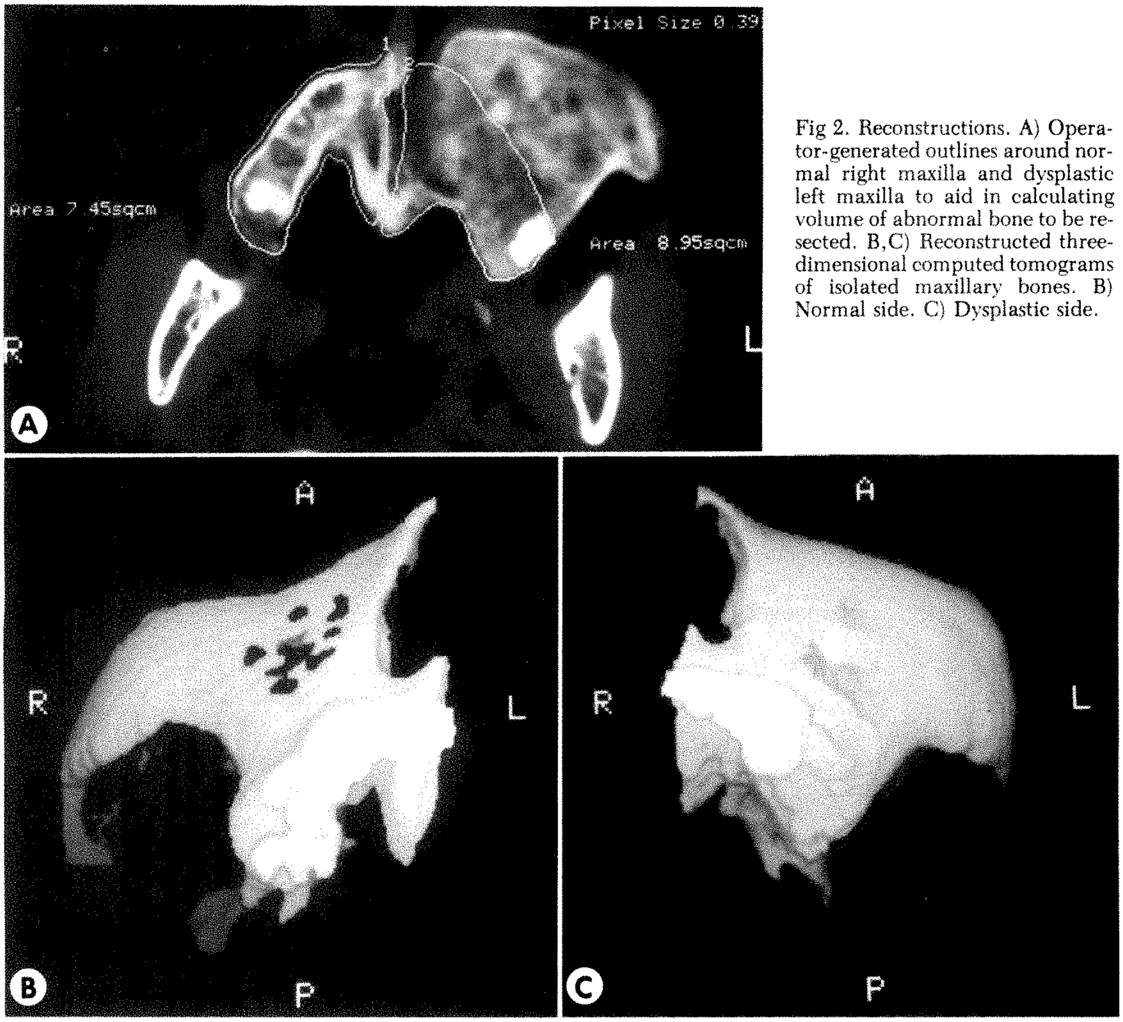

Fig 2. Reconstructions. A) Operator-generated outlines around normal right maxilla and dysplastic left maxilla to aid in calculating volume of abnormal bone to be resected. B,C) Reconstructed three-dimensional computed tomograms of isolated maxillary bones. B) Normal side. C) Dysplastic side.

traoperatively in assessing the limits and volume of bony contouring.

Fibrous dysplasia is a congenital, nonhereditary, benign bony lesion characterized by an idiopathic proliferation of fibro-osseous matrix in the long bones and/or calvaria of affected individuals.[1] While it may present as monostotic or polyostotic disease, the monostotic form is four times more common. Approximately one third of patients with monostotic disease will have craniofacial involvement, usually of the maxillary, frontal, or sphenoid bones. These patients may present with a myriad of cervicofacial symptoms including sinusitis, epiphora, nasal obstruction, hearing loss, and blindness.[2,3]

Surgical therapy is indicated in cases of cranial nerve compression or in cases of severe cosmetic deformity for which the patient desires intervention. Spontaneous regression is rare. Radiotherapy is ineffective and has been associated with malignant transformation. Recommended surgical intervention ranges from simple bony contouring to removal, remodeling, and replacement of dysplastic bone. Recurrent dysplastic enlargement will occur in approximately 25% of lesions treated by simple contouring of the affected bone.[4]

Given the complexity of overlapping structures on craniofacial plain films and the sometimes varied appearance of this type of osseous metaplasia, CT has proven useful in 1) establishing the diagnosis and 2) defining specific bony involvement as well as the extent of disease.[5] In addition, CT data now provide the material from which multiplanar and 3-D images can be generated and manipulated to assist in preoperative planning and follow-up.

While axial CT affords detailed bone imaging, reconstructive surgeons have documented the advantages of multidimensional CT scanning in providing a global anatomic image of complex craniofacial disorders.[6,7] We present a case of hemifacial maxillary and sphenoid fibrous dysplasia with severe facial asymmetry in which the use of 3-D CT imaging aided greatly in patient counseling, preoperative planning, operative resection, and postoperative follow-up evaluation.

CASE REPORT

A 30-year-old woman presented for evaluation and treatment of asymptomatic left facial asym-

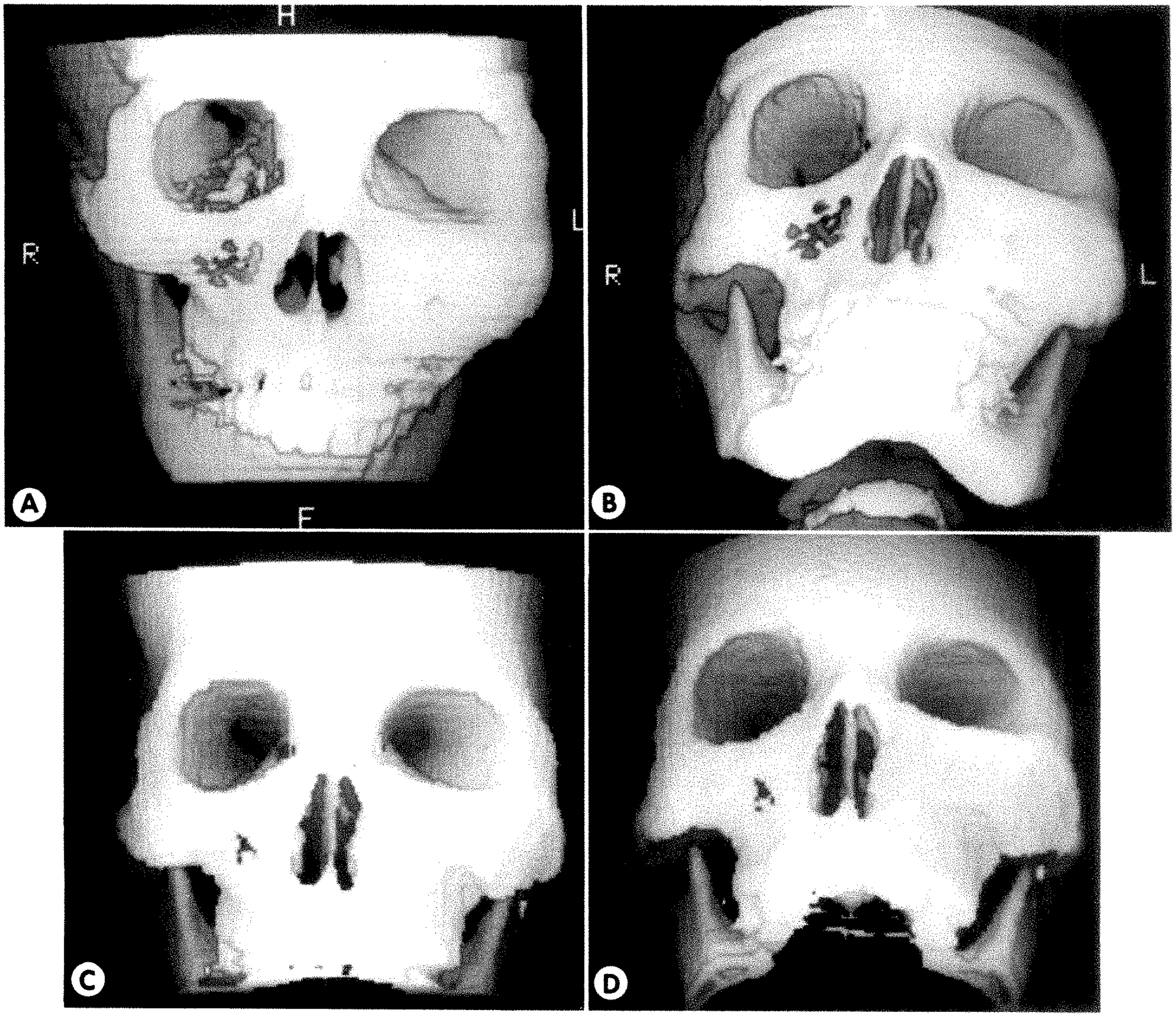

Fig 3. Reconstructed three-dimensional computed tomograms of A,B) preoperative deformity and C,D) postoperative results.

metry (Fig 1A). The deformity had progressed since childhood but had remained stable over the past 10 years. She denied any symptoms of diplopia, epiphora, pain, nasal obstruction, or paresthesias. She had no history of skin lesions, precocious puberty, or other endocrine abnormalities. Physical examination was confirmatory for the left facial asymmetry without cranial nerve findings or other abnormalities. Her metabolic evaluation was normal, including a normal alkaline phosphatase level.

Computed tomographic scanning was performed on a Picker 1200 SX scanner in axial 4-mm scans with a 1-mm overlap with use of a modified bone algorithm. Processed images were then transferred to an independent work station (Maxiview, Dimensional Medicine, Inc, Minnetonka, Minn) for the generation of 3-D–rendered preoperative and postoperative images. These were created by establishing a region of interest around the area of each axial CT image to be included in the 3-D reconstruction.

The preoperative CT scans show the typical diffuse sclerosis and enlargement of affected bone in this patient with involvement of the entire left maxilla, the greater wing of the sphenoid, the body of the left zygoma, and the inferior aspect of the left frontal bone (Fig 1B,C). Hypothetical postoperative images were created preoperatively by using a cursor and track ball system on each image to be included in the 3-D–rendered volume. The area of the maxilla remaining on each "resected" image could be compared to the normal right side either by appearance alone or by outlining the same region of the normal (right) side, then by calculating and comparing both the normal and abnormal areas (Fig 2A). In addition to being viewed in continuity with the normal facial bones and skull, the affected area could also be viewed in isolation. Complete or isolated 3-D renderings could be rotated in any plane or at any angle to view the deformity from any perspective (Fig 2B,C).

In preoperative consultation with the patient, the options discussed included simple bony contouring

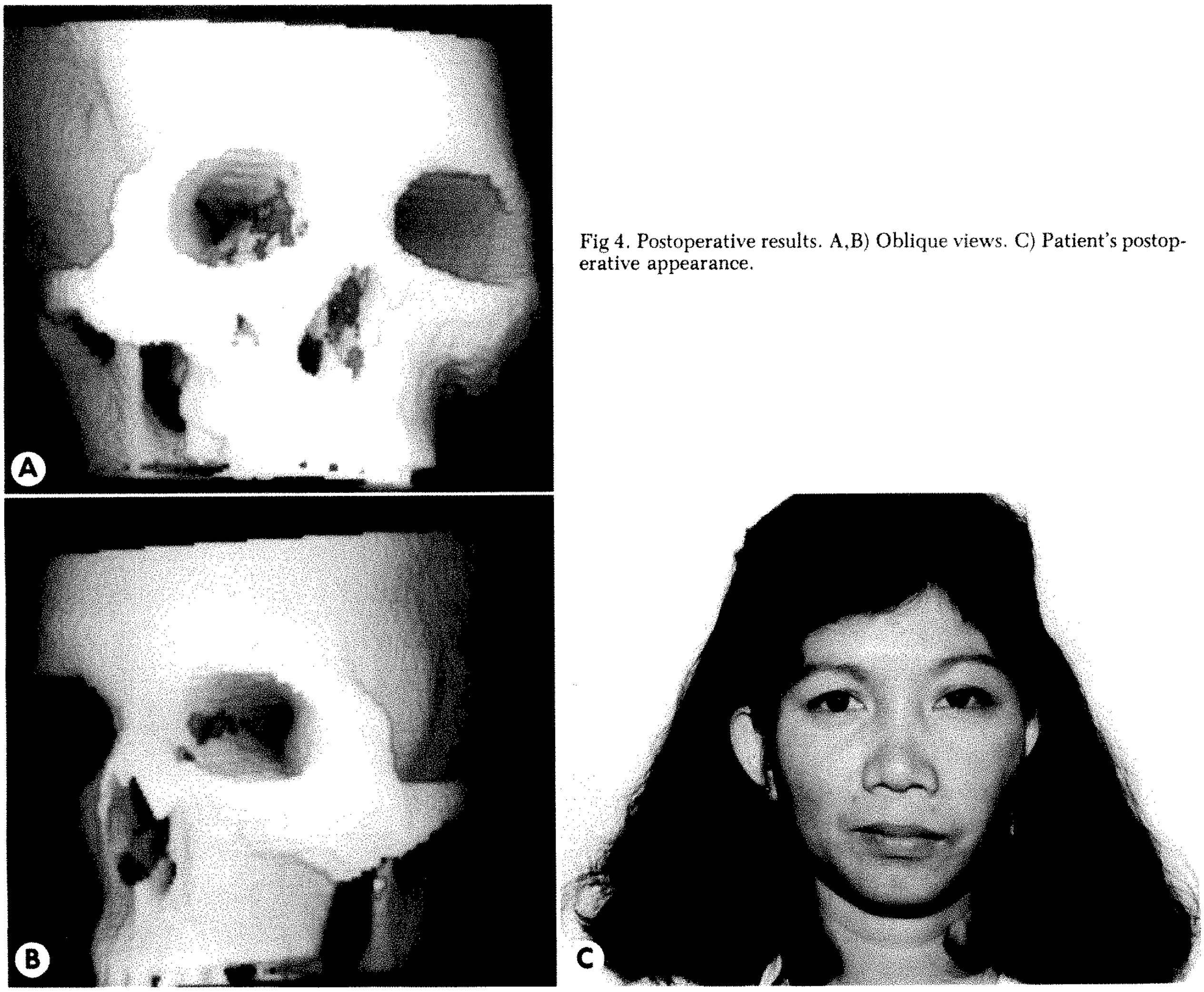

Fig 4. Postoperative results. A,B) Oblique views. C) Patient's postoperative appearance.

of the maxilla versus resection and remodeling of the maxilla together with the orbital floor and frontal bone via a craniofacial approach. With the aid of MPR-CT imaging, the patient was able to visualize the extent of bony involvement as well as the areas of planned surgical correction. She elected to proceed with the less radical contouring operation with the goal of alleviating the cosmetic deformity. The procedure was performed through a limited facial degloving approach, exposing the affected left maxilla and lateral buttress. Facial symmetry was achieved with sculpturing osteotomies and cutting bur drilling of the dysplastic maxilla.

A review of postoperative 3-D images shows that much of the bone was excised from the anterior-inferior and middle aspects of the maxilla (Figs 3 and 4A,B). Remodeling of the left lateral buttress and face of the left maxilla has approached the contour of the normal right maxilla (Fig 4C).

DISCUSSION

Reconstructive 3-D CT scanning has become a valuable adjunct in the imaging of craniofacial and midfacial skeletal deformities. Reconstructive surgeons have documented its usefulness especially in determining the volume and shape of bone grafts needed for reconstruction of defects after complex facial trauma, tumor ablation, and craniofacial surgery for congenital disorders, as well as determining orbital volume and complex temporomandibular joint disorders.[5,6]

In this case, surgical options included 1) simple contouring of the maxilla and 2) subtotal craniofacial resection of the dysplastic bone with remodeling and replacement of the affected segment. In planning the surgical approach, axial CT delineated the extent of maxillary and sphenoid dysplasia quite well. In consultation with the patient, however, MPR-CT imaging proved to be invaluable in providing a global, lifelike view of the facial skeletal abnormality to the patient. By seeing rotation and cutaway views of the craniofacial complex, the patient was able to visualize the extent of abnormal bone and was more easily able to make an informed decision concerning the options of surgical resection versus contouring. The patient in this case elected to alleviate the cosmetic deformity with simple contouring of the maxilla rather than undergo a more radical resection with remodeling and replantation.

The 3-D views provided a conceptually superior, nonsegmental image of the lesion to the surgeon. Although no volume measurements of the dysplastic bone were calculated, repeated intraoperative reference to the image was used to aid in the reshaping and sculpting of the lateral zygomaticomaxillary buttress on the affected side. We believe that 3-D reconstructed images are of value in selected cases of craniofacial fibrous dysplasia in which bony contouring is planned to achieve facial symmetry.

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CONFERENCE ON ASSISTIVE LISTENING DEVICES
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IMAGING CASE STUDY OF THE MONTH

METASTATIC TUMOR PRESENTING AS CHRONIC OTITIS AND FACIAL PARALYSIS

DAVID S. MARTIN, MD
JAMES BENECKE, MD
COREY MAAS, MD
ST LOUIS, MISSOURI

CASE REPORT

A 71-year-old man presented with a 4-week history of right-sided facial paresis of insidious onset. He reported a long history of intermittent otorrhea that began after a traumatic perforation of the tympanic membrane. The patient denied tinnitus or vertigo. Additionally, he relayed a history of right shoulder pain and auricular paresthesia.

The patient had a medical history of recurrent pneumonia, chronic obstructive pulmonary disease, and peptic ulcer disease. He had undergone partial gastrectomy and saphenous vein stripping in the past. He had a 60-pack-year history of smoking and admitted to occasional use of alcohol.

On physical examination, a grade 6 (House-Brackmann) right-sided facial nerve paralysis was noted. His tongue deviated to the right. The remainder of the findings on cranial nerve examination were unremarkable. Otorrhea was observed from the right ear with ceruminous debris filling the right external auditory canal. The left ear appeared normal. The remainder of the examination findings of the head and neck were normal.

The patient's laboratory values were unremarkable. Cultures taken from the right external auditory canal failed to grow significant organisms. Changes consistent with chronic obstructive pulmonary disease and perihilar densities were observed on chest radiographs. Audiometry revealed bilateral severe high-frequency sensorineural hearing loss and a flat tympanogram on the right. Electronystagmography showed no response on the right.

A computed tomogram of the temporal bone accompanied the patient and demonstrated opacification of the mastoid air cells on the right and evidence of bone destruction involving the mastoid (Fig 1A). A mass inferior to the mastoid was also observed (Fig 1B). Gadolinium-enhanced magnetic resonance imaging demonstrated the extent of the mass from the base of the styloid process to the mid-

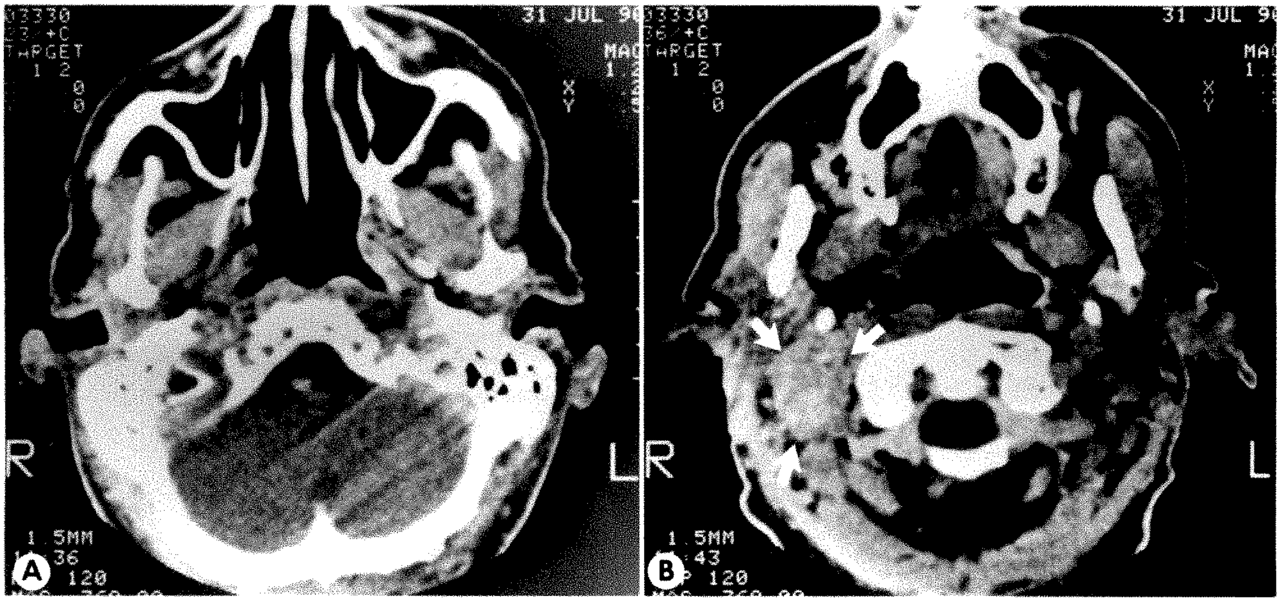

Fig 1. Axial computed tomograms. A) Demonstrating right mastoid opacification and adjacent bone destruction. B) At level of styloid process, showing mass (arrows).

From the Departments of Radiology (Martin) and Otolaryngology-Head and Neck Surgery (Benecke, Maas), St Louis University Medical Center, St Louis, Missouri.

REPRINTS — David S. Martin, MD, Dept of Radiology, St Louis University Hospital, 3635 Vista at Grand, St Louis, MO 63110-0250.

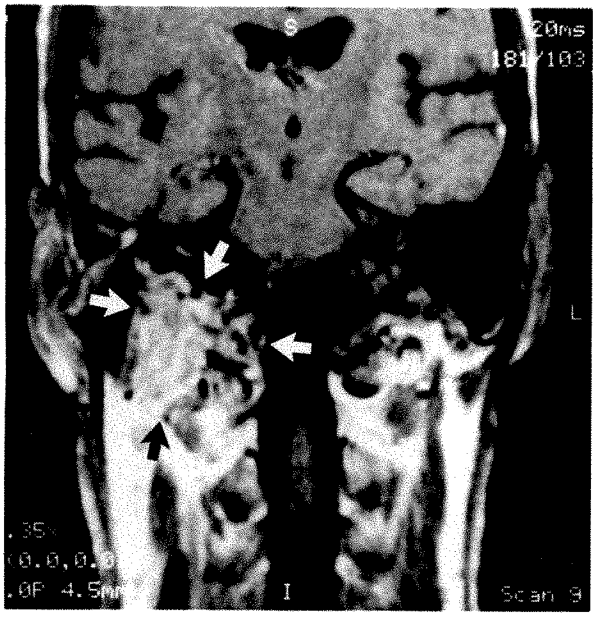

Fig 2. Coronal T1-weighted magnetic resonance image with gadolinium enhancement illustrates extent of mass (arrows).

dle ear cavity (Fig 2). A subsequent computed tomogram of the chest demonstrated a left lower lobe mass (not illustrated) that was determined to be small cell carcinoma of the lung.

DISCUSSION

When one is confronted with a patient who has otorrhea and a facial paralysis on the same side, the immediate thought is that this represents a complication of chronic suppurative otitis media. Such a complication mandates a careful evaluation and expeditious surgery.[1]

Of course, one also is compelled to formulate a differential diagnosis in such a situation. Primary tumors of the skull base such as paragangliomas and schwannomas rarely produce a draining ear, and infrequently present with a facial paralysis. Malignant tumors of the temporal bone are rare, but adenocarcinoma and other glandular tumors could potentially cause facial paralysis and otorrhea.[2] Finally, metastatic tumors must be given consideration.[3] The history of a known primary malignancy will usually lead to this diagnosis.

This patient had symptoms due to a huge tumor involving the temporal bone. The tumor had destroyed the stylomastoid foramen, producing the facial paralysis. It had also eroded into the middle ear space and through the tympanic membrane, presumably resulting in otorrhea. The extensive bone destruction shown by computed tomography and the extensive mass demonstrated by magnetic resonance imaging excluded suppurative disease. The chest radiograph provided the clue that the patient's symptoms were due to a malignant process originating in the lung.

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FIRST EUROPEAN SYMPOSIUM ON PEDIATRIC COCHLEAR IMPLANTATION

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Ann Otol Rhinol Laryngol 101:1992

PATHOLOGY CONSULTATION

NECROTIZING SIALOMETAPLASIA

NOUR SNEIGE, MD
JOHN G. BATSAKIS, MD
HOUSTON, TEXAS

Necrotizing sialometaplasia of salivary tissues is a vascular-based (lobular infarct), benign, and often self-limited disorder. Preponderantly a lesion of palatal salivary glands, it can involve any salivary gland, and it may be mistaken for carcinoma. Adherence to histopathologic criteria should obviate this mistake.

Necrotizing sialometaplasia is a benign, reactive, inflammatory, and usually self-limited disorder of salivary tissues with clinical and histologic features that simulate malignancy, particularly mucoepidermoid and squamous cell carcinomas.[1] Preponderantly a lesion of the minor salivary glands of the palate, necrotizing sialometaplasia can be found in any salivary tissues, including the major salivary glands[2,3] (see Table[2]). In the oral cavity, it has an estimated prevalence of 0.03% of all lesions submitted to biopsy — certainly an underestimation.[4]

Although squamous metaplasia can be found in several forms of inflammatory and neoplastic disorders of the salivary glands, necrotizing sialometaplasia is a histologically distinctive type with specific diagnostic criteria.[1-3] These are 1) lobular necrosis of salivary tissue (Fig 1A), 2) a time-variable prominence of subsequent granulation tissue and acute and chronic inflammation (Fig 1B), 3) squamous metaplasia conforming to duct and/or acinar outlines (Fig 1B,C), and 4) maintenance of the salivary lobular morphology (Fig 1B). Adherence to these criteria, especially the last one, excludes other forms of squamous metaplasia, such as that occurring at the periphery of a necrotic cyst (neoplastic or otherwise) and pseudoepitheliomatous hyperplasia extending into ducts.

An ischemic basis for necrotizing sialometaplasia is the most accepted one.[2,3,5-7] This causation is supported not only by experimental evidence[8] but also by clinical and histopathologic observations of the lesions following surgical procedures (Fig 2) or radiotherapy at the involved site and an association with thrombosis, Buerger's disease, and emboli.[3] There is also a histologically analogous lesion found adjacent to infarcted areas of the prostate gland.[7]

In either minor or major salivary glands, the basic histologic lesion is an infarct of salivary lobules with subsequent repair and metaplasia. The arterial supply of the palate's minor salivary glands is the anterior palatine artery. This vessel enters through the rigid major palatine foramen. The major branches course anterolaterally, with only small branches passing medially to the areas in which necrotizing sialometaplasia has been most often described. The blood supply is vulnerable at the foramen and also distally, where any agent capable of producing compromise or vascular injury can lead to infarct. In the major salivary glands, the arterial vessels follow and accompany subdivisions of the excretory duct system so that each salivary lobule has a separate and distinct blood supply. Even within the lobules, vascular territories are also characteristically distinct, with each culminating in a series of end vessels. Disruption of this blood vasculature after surgical procedures in the major salivary glands is self-evident and accounts for 86% of the reported cases.[3] A similar postoperative sequence is seen in

SITES OF INVOLVEMENT OF NECROTIZING SIALOMETAPLASIA (N = 184)

Site	*No.*	*% of Total*
Palate		
Hard	100	
Soft	10	
Junction	25	
Not specified	7	
Total	142	77.2
Nonpalate oral		
Lower lip	7	
Retromolar	5	
Tongue	2	
Buccal	2	
Mucobuccal fold	1	
Tonsillar fossa	1	
Total	18	9.8
Major salivary glands		
Parotid	14	
Sublingual	1	
Submandibular	1	
Total	16	8.7
Other head and neck		
Nasal cavity	5	
Maxillary sinus	1	
Larynx	1	
Incisive canal	1	
Total	8	4.3

From data presented by Brannon et al.[2]

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

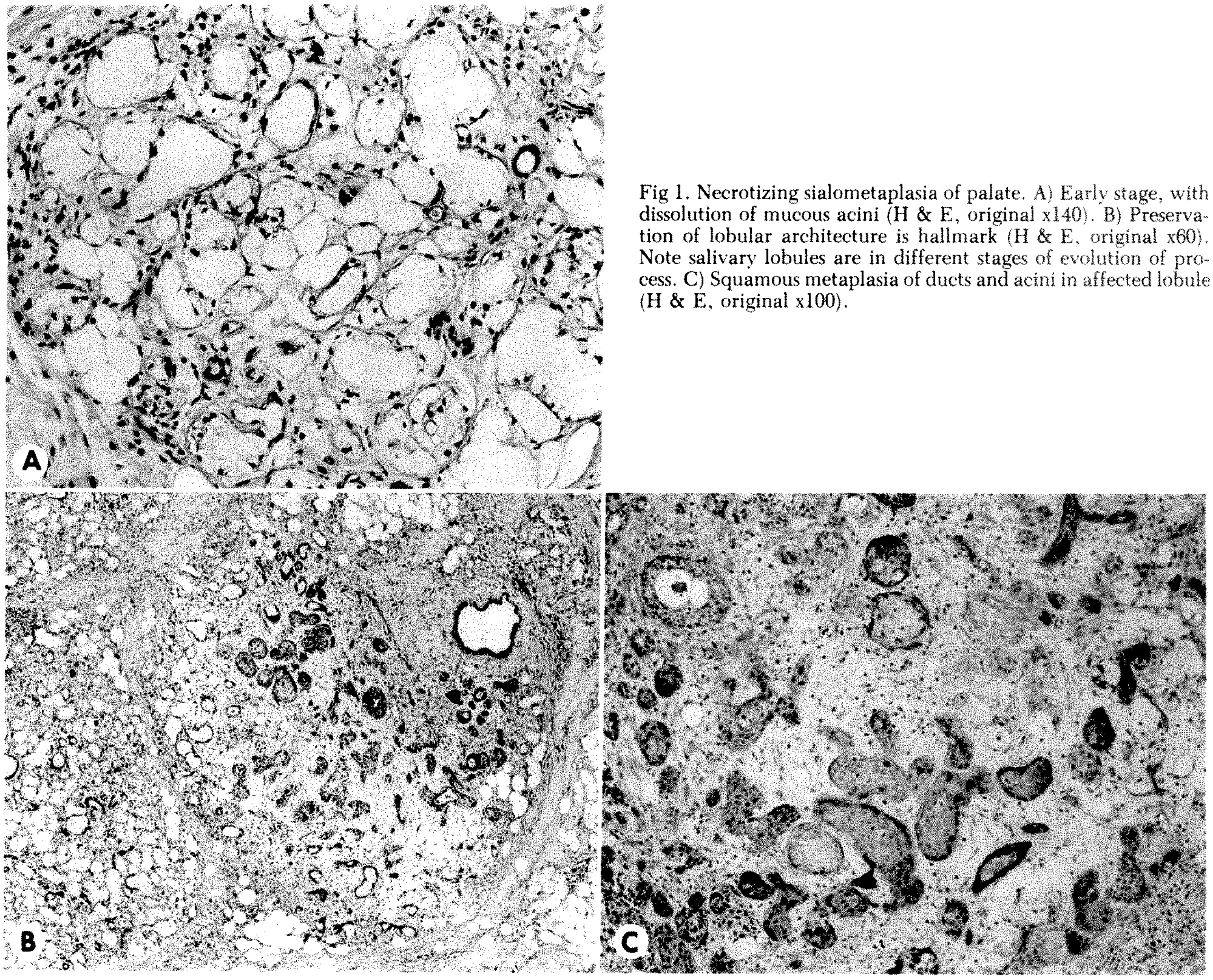

Fig 1. Necrotizing sialometaplasia of palate. A) Early stage, with dissolution of mucous acini (H & E, original x140). B) Preservation of lobular architecture is hallmark (H & E, original x60). Note salivary lobules are in different stages of evolution of process. C) Squamous metaplasia of ducts and acini in affected lobule (H & E, original x100).

necrotizing sialometaplasia of the upper airway.[3]

While prior surgery is not often a culprit in necrotizing sialometaplasia of the palate, subtler forms of vascular compromise are still held ultimately responsible. These include dental infections, ill-fitting dentures, and localized mucosal edema.[2]

No age is immune, but the average age at time of diagnosis is 46 years.[2] Males are afflicted twice as often as females and whites outnumber blacks by a ratio of 5:1.[2] As the Table indicates, the majority of cases are found on the posterior hard palate, with the junction of hard and soft palates the second most common site. Nearly three quarters of the palatal lesions are unilateral, and a tenth are bilateral; a lesser number are said to be midline.[2] Since salivary tissue is not normally found in the midline of the hard palate, lesions found there are likely due to extension or coalescence of unilateral or bilateral lesions. The parotid gland is the major salivary gland most often reported as being involved.[3]

In mucosal sites, necrotizing sialometaplasia most often presents as a deep-seated ulcer, with or without an antecedent swelling or mass. A mass accounts for only about a third of reported cases, including mucosal and nonmucosal parenchymal sites. Painful lesions are about twice as common as those without symptoms. Paresthesias or anesthesia may also be noted. Brannon et al[2] indicate that bony involvement is not generally described or to be expected, but its presence (rare) does not preclude the diagnosis of necrotizing sialometaplasia.

Anneroth and Hansen,[6] subscribing to the vascular cause for necrotizing sialometaplasia, emphasize that the different stages of evolution of the lesion often overlap, and can occur simultaneously in different areas of the affected salivary tissue. The severity of the infarct also varies. Extensive infarct can lead to a sequestration of necrotic areas and to ulcer formation with the craterlike defects found in some cases of the disorder. The size of the lesions is dependent on the number of affected lobules and the severity of the necrosis. As a result, necrotizing sialometaplasia at any salivary site can be smaller than 1 cm or larger then 5 cm. In the series reported by Brannon et al,[2] the average size was 1.8 cm.

The healing process in necrotizing sialometaplasia includes repair of both the ulceration (if present) and of the damaged salivary tissues. Proliferation of

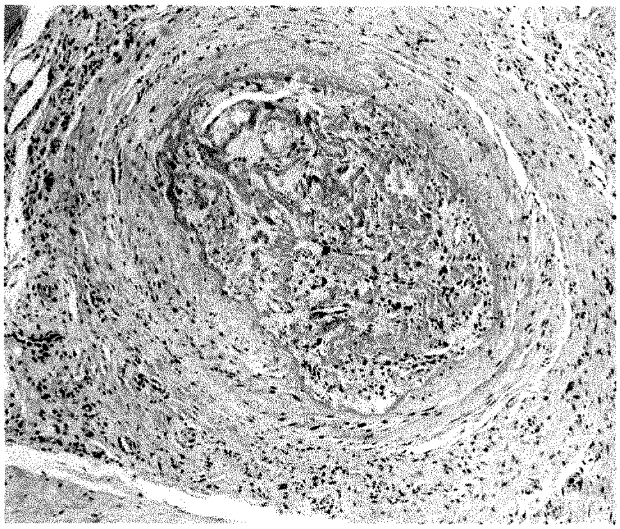

Fig 2. Palatine artery with thrombosis adjacent to necrotizing sialometaplasia (H & E, original x140). Specimen is from reexcision of pleomorphic adenoma-bearing area.

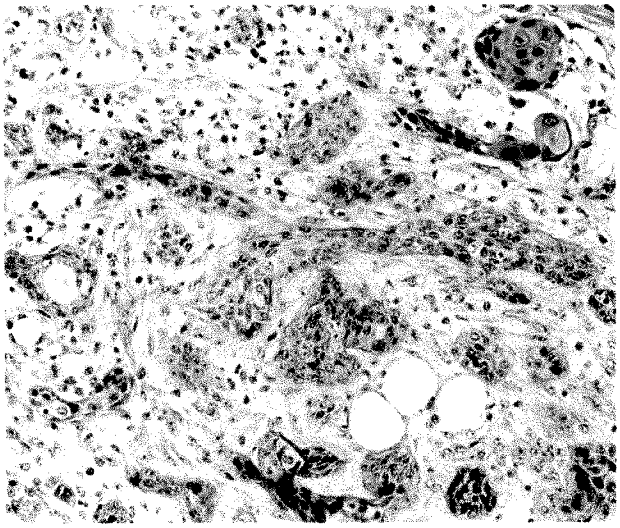

Fig 3. Metaplastic ducts and acini in various degrees of cellular differentiation (H & E, original x140). Note interepithelial histiocytes in this salivary lobule.

surface mucosal cells covers the epithelial defect and often presents as a form of pseudoepitheliomatous hyperplasia. Regeneration of affected ducts and acini is never complete, but the metaplasia of small ducts and acini can be associated with prominent nuclei and frequent mitotic figures. It is the combination of an ongoing necrosis and repair that may lead to the mistaken diagnosis of malignancy if the specific criteria are not adhered to (Fig 3).

Necrotizing sialometaplasia generally heals spontaneously without treatment within 6 to 10 weeks.[2,6] Treatment of symptoms is indicated for patients with painful lesions.[2]

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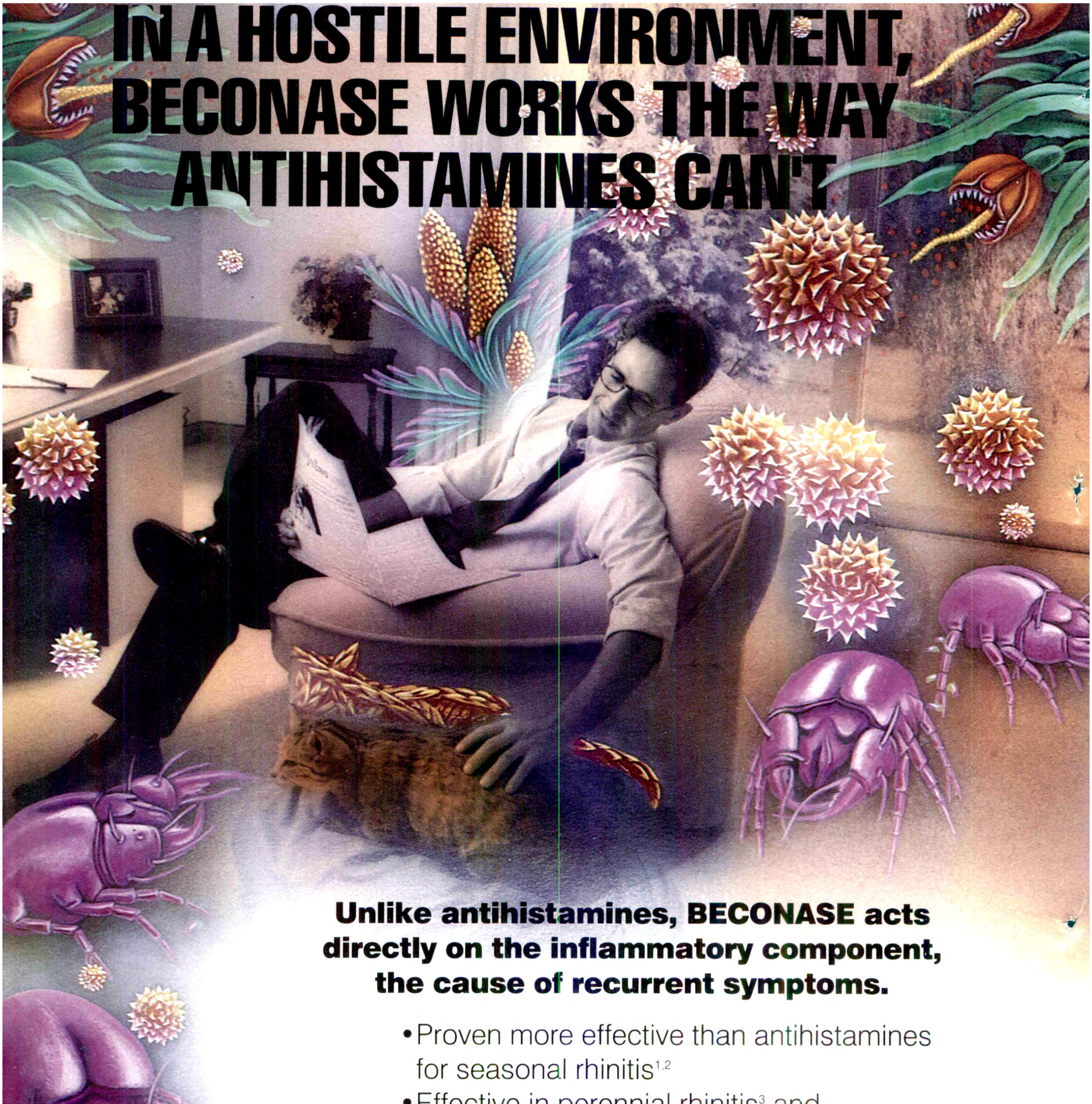
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This article originally appeared in March 1937, Volume 46, No. 1, pages 79-86, and is reproduced here in its entirety.

SURGICAL REMOVAL OF THE SPHENOPALATINE GANGLION*

REPORT OF THREE OPERATIONS; ELABORATING AN ORIGINAL TECHNIC TO EXPOSE THE PTERYGOPALATINE FOSSA, COMMAND THE INTERNAL MAXILLARY ARTERY AND ITS TERMINALS AND THE INFRAORBITAL NERVE AND ITS BRANCHES

EDWARD CECIL SEWALL, M.D.†
SAN FRANCISCO

The importance of a trans-antral surgical approach to the sphenopalatine fossa was suggested to me by the fact that

1. Stubborn cases of fifth nerve type neuralgia in which the gasserian ganglion has been severed have been relieved by anesthesia or destruction of the sphenopalatine ganglion.

2. Infection in the sphenopalatine fossa, usually the result of injections, is not uncommon and has been fatal in spite of surgical measures heretofore employed.

3. The whole extracranial part of the infraorbital nerve is available.

4. The internal maxillary artery and most of its branches can be isolated and ligated.

5. The various branches of both the infraorbital nerve and the sphenopalatine ganglion are at hand for surgical disposition.

6. The sphenoid sinus can be entered and operated upon.

7. There are many other vital structures in the neighborhood that skillful surgery may approach.

8. The orbit is surgically available from below, even to the apex. This feature has been taken advantage of through a different incision in my recently published technic for the relief of pernicious exophthalmos.

In 1926[1] I published an operative approach by way of the maxillary sinus to the pterygopalatine and infratemporal fossæ. It was subsequently learned that Carnochan,[2] in 1858, had followed the infraorbital nerve from its exit at the infraorbital foramen to the foramen rotundum. His approach differed in that an incision was made through the cheek and the nerve was followed with sacrifice of the orbital floor.

---

*Presented before the 58th annual meeting of the American Laryngological Association, Detroit, Mich., May 25, 1936.

†From Department of Otolaryngology of Stanford University with assistance of the Rockefeller fund.

In 1929 Vogel[3], following precisely by technic in the manner of approach, elaborated the details of dissection in the fossa and removed the sphenopalatine ganglia in nine living patients. He was interested in determining the condition of the ganglion in ozena and came to the following conclusions: 1. In genuine atrophic rhinitis there is isolated atrophy of the sphenopalatine ganglion. 2. Its disease is secondary to the ozena. 3. Because of the insignificance of the disturbance caused by its removal, he believes that its functions are quickly taken over by other nerves (perivascular branches).

Gussenbauer, Friedlander, Kocher, Lucke, Lossen, Braun, Krause and Lever all approached the pterygopalatine fossa from the side by a preliminary resection of either the temporal arch or the entire malar bone.[4]

In 1931, Braenckner[4] described an approach from the side, through the skin, that included removal of the wall of the antrum.

In 1935, Auerbukh et al.[5] divided prior operations into three groups according to the approach: Orbital, transantral, zygomatic. They describe an ingenious method which has been worked out on the cadaver. It gains access to the pterygopalatine fossa from below by resecting the hard palate.

A number of fatal infections in the pterygopalatine fossa have occurred following injection of anesthetics or other fluids. These accidents have followed injections by way of the skin in the region of the zygoma and also those made through the mouth via the postpalatine canal or around the alveolar process.

The approach through the antrum, if employed early in such serious infections, should offer adequate surgical control.[6]

The technic of the operation, as first described by me in 1926, is given below with subsequent modifications.

The work is done under sodium amytal and scopolamin and morphin sedation and local anesthesia.

The Caldwell-Luc technic is used in opening widely through the canine fossa into the antrum, and from the antrum under the inferior turbinate into the nose.

The mucosal lining of the posterior wall of the antrum is circumbscribed by an incision down to the bone and is removed. The rest of the mucosa is not disturbed unless disease indicates the necessity for its removal. The posterior bony wall of the antrum is next removed and the periosteum enclosing the contents of the pterygopalatine fossa exposed. A strong solution of cocain is applied to this periosteum. Injection of the space for anesthesia may damage an artery and cause delay.

The periosteum is incised carefully and the underlying parts dissected with blunt instruments.

The internal maxillary artery is seen pulsating in a bulging arc across the field. It is followed to the nose without injury.

The infraorbital nerve is discovered lying across the depths of the upper part of the operative field. It is followed toward the foramen rotundum, which can be clearly seen.

Extending downward and medially from the infraorbital nerve near its exit from the foramen rotundum, the sphenopalatine ganglion is found. It lies just outside the nose, anterior to the base of the pterygoid process and almost directly posterior to the internal maxillary artery as it approaches the sphenopalatine foramen. (Fig. 1.)

The ganglion is freed by careful dissection with small hooks and forceps and is removed after its various branches have been severed. The artery or any of its branches may be ligated if required.

The infraorbital nerve may be severed at the foramen rotundum if advisable. The wound is closed as usual.

I am herewith reporting two cases operated upon in this manner. One of them had both ganglia removed at successive operations, more than three years apart.

REPORT OF CASES

CASE 1.—Male, 30 years of age. First consulted me October 30, 1930. An agreeable young man, with strong personality evident under a modest demeanor. Complaint: Severe pain in upper jaws and teeth, over, about and in both eyes, roughness of eyelids during an atttack when pain also radiates down the arms and extends even into the legs. Nauseated when pain becomes bad. Allergic history and diagnostic testing negative.

Has had a watery discharge from the nose that is more or less constant. Has about one cold a year. Ordinarily breathes freely through the nose, which swells and becomes stuffy prior to an attack of pain. Radiographs have shown no evidence of sinusitis. Tonsils have been removed and hearing is good. There is some tinnitus during attacks. No arthritis and patient is otherwise well.

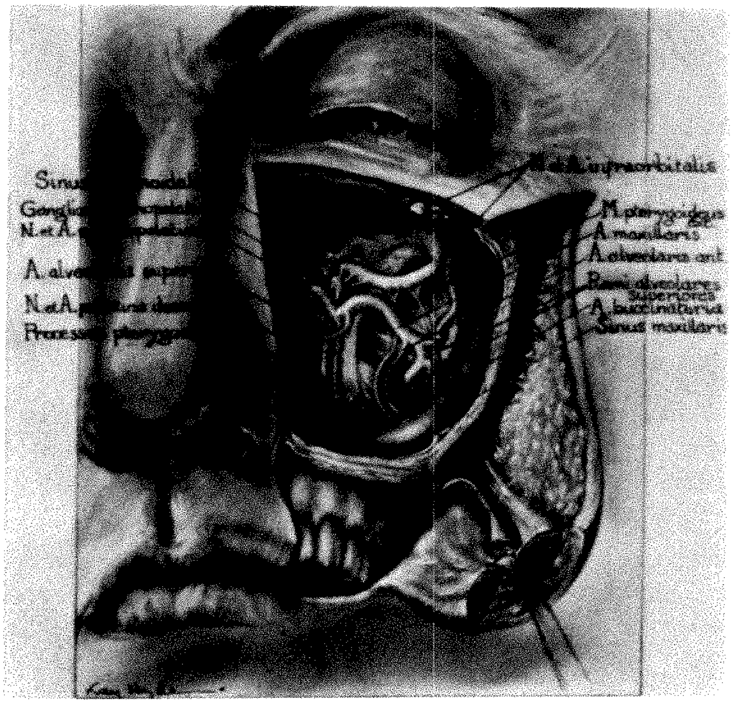

Fig. 1. The wide exposure shown here is, of course, from a laboratory dissection. It, or some modification, may be employed when malignancies or destructive processes minimize the importance of postoperative disfigurement. However, the approach described in the text is according to the Caldwell-Luc technic.

Examination disclosed nothing of importance except that cytologic study of the nasal discharge disclosed numerous polymorphonuclears on the right side. Test of the right antrum showed macroscopically sticky mucus and microscopically a few mononuclear and polymorphonuclear leucocytes. The left antrum showed only a few mononuclears. Operative procedures to clear up the low grade sinus infection were of no avail in relieving the distressing and incapacitating pain.

His condition finally became so pitiful and the employment of drugs so alarming that it was decided to remove the sphenopalatine ganglion on the left or worse side. This was done January 12, 1931, according to my technic which has been described. He left the hospital without pertinent incident on January 30, 1931.

His letter of February 9th says: "The pain in the left cheek, nose, eye and upper jaw is slowly going away, but is still constantly discomforting and at times unbearable. Every few moments there is some sort of disturbance in the left cheek or left upper lip as though a hot needle were passing through it, or sometimes like a bee buzzing in a flower. The needle effect is painful; the buzzing sensation is only uncomfortable. The left eye aches and is slow to adjust itself to the light in the morning. The teeth under the incision ache most of the time, more after eating and drinking. The left roof of the mouth is numb, yet at times there is feeling of a hot needle running back and forth in it. The external swelling is still apparent but gradually reducing. I believe that as soon as the operative pain disappears there will be no further trouble."

In another note of March 18, 1931: "I am working eight hours a day. We are going out to dinner, playing cards, and so on. I am sorry the pain does not go away. The left cheek, lip and eye continue disturbed. The headache has never left. It is intense and constant. We have done everything we can, so I am going right ahead disregarding the pain as far as possible."

On April 30, 1931, he again writes: "The operation has proved to be a complete success. There is none of the old pain in the left side. The nausea has completely disappeared. There has been no more pain in the arms or fingers. Occasionally the old pain comes back full length in both legs. All medicines have been discontinued. Recovery from the operation has been very slow. I had the left antrum washed out. The water returned clear. Aside from the slow recovery I am delighted with the operation. The pain has stopped completely on the left side. If the right side continues painful would you recommend the removal of the right ganglion? It is fine to be at work again."

September 16, 1931, he says: "I am writing to tell you that the removal of the left ganglion has given complete relief from pain on left side and to ask your advice about the right side. Numbness on the roof of the mouth is noticeable only in eating; then pressure on the teeth under the incision is unpleasant.

"The right side is the same as it has been for the past ten yeaers, and I am often tempted to ask you to remove the ganglion on that side. The right eye burns and the lid feels rough and the surrounding area feels bruised. Intermittently there is pain in the right forehead, a headache and pain in the right jaw the same as toothache. The pain in the jaw skips around, sometimes upper, sometimes lower, usually front upper and back lower. In a period of pain of more than usual severity I am nauseated. Flare-ups of severe pain last a day or two. There is practically no freedom from pain. The use of the eyes seems to make the pain worse. Long auto or train rides invariably set it off. Reading, playing cards or tennis do likewise. The situation is entirely different than before the removal of the left ganglion. Then it was impossible, now it is annoying. On account of daily swimming and tennis, I am in splendid condition. I would appreciate very much your advice."

I did not hear again from the patient until 1934, when the following letter came:

June 12, 1934. "For the past several months the pain on the right side of my head has been very severe. The left side is entirely free from pain and there are no ill effects from removal of the ganglion. The right side, however, is very bad. The symptoms are the same as for years except that the pain has been more constant, more severe, there being practically no free periods. The pain is in both upper and lower teeth on the right side, the right eye and in the right forehead above and about the eye. The right eyelid burns and during an attack the eye waters. When the pain is severe I am nauseated, recently vomiting for about three days. Three weeks ago the doctor here cut a window in my right antrum. I am writing to know how you would feel about removing the right ganglion for me. If the pain continues to be as severe, I must do something to relieve it."

June 29, 1934. My answer: "Your letter has left me in a quandary as to how to advise you. I am happy that what I did for you has given you so much relief. I admit that I was loathe to do that work and am even more anxious to avoid working on the other side. I think that in as much as you have had an operation recently you had better give it time to see what the ultimate result will be."

July 16, 1934. Without having consulted me further at this time he had another surgeon remove his right sphenopalatine ganglion.

Following this operation there was no change in the character or severity of the pain in the right side of the head. Pain in the legs increased and pain in the hand returned. There has been no numbness about the head similar to what followed the operation on the left side. He was advised by a neurological surgeon to have something done to the right cervical sympathetics.

December 5, 1934. The patient consulted me again He was in great distress with the right side of head and body as outlined. It had become necessary to take opiates constantly; he was taking morphin and codein up to 12 grains per day; also other opiates at intervals.

January 21, 1935. I operated upon the right sphenopalatine ganglion and he left the hospital in about ten days without unusual incident.

February 11, 1935. A letter from Carmel says: "We made the trip down as well as could be expected. While the eye, cheek incision and jaws are full of pain, it is easier to stand. You will be glad to know that I went twelve hours last night between hypos. We have this thing beaten. All that is necessary is to hang on for a little while."

March 4, 1935. "I have been home two weeks and suppose I am making fair progress. The right eye, cheek and lip are still sensitive to touch. I have not been to the office yet, though have worked in the garden some."

February 25, 1936, he writes: "I am happy to report to you that the work you did in January, 1935, has given complete relief from the old pain. I am now free from the old pain on both sides. I have since had no craving for narcotics nor have I had any in any form. I am working every day and have gained thirty pounds."

May, 1936, he consulted me. He is a healthy appearing, hard working, successful business man. At intervals he has pain and disturbance in the right cheek. It seems to have some relation to taking cold. Stuffiness of the nose precedes the attacks. We, therefore, cannot call him well. He is infinitely better, however. Except for some altered sensation to touch over the cheek and hard palate, there is no evidence of nerve disturbance.

Both sides of the nasal fossæ are equally sensitive to touch. The turbinates on both sides shrink immediately and normally where neosynephrin is applied.

The sympathetic control was apparently quickly re-established. This has been described by others and ascribed to the assumption of control of the sympathetic fibers following the blood vessels.

The following information was contained in a note received received from the patient in December, 1936: He is almost over his troubles, is working every day and quite a few evenings, including a lot of traveling on business.

Case 2.—Mrs. B., age 55, entered Stanford Clinic July, 1931. Complained of pain in the left side of face which had persisted for four years. Pain began in left zygomatic region, gradually increasing in severity. After three months the left gasserian ganglion was operated upon. This relieved the stabbing feature but dull pain persisted. A sympathectomy was done two and one-half years ago and this was followed by injections without relief. The patient was practically helpless.

A nervous woman, complaining bitterly of pain. Showed no organic disturbance except for loss of all sensation over the region of distribution of the left fifth nerve. Diagnosed trigeminal neuralgia, with confusing psychic disturbances.

October 29, 1932. Dr. Reichert did a diagnostic block of the left cervicothoracic sympathetic chain. There was some relief. On May 22, 1933, this was followed by removal of the cervical sympathetic chain and carotid sinus.

August, 1935, left sphenopalatine ganglion was concainized, without improvement. The sphenopalatine ganglion was later injected with novocain by Dr. Rixford. There was definite temporary relief.

October 16, 1935, I removed the left sphenopalatine ganglion according to the technic described. There was some pain complained of when the ganglion was manipulated. She was discharged from the hospital without intervening incident, on October 20, 1935.

April 9, 1936. A letter from Dr. Rixford tells the following story: "Here are the results of my examination: Complete anesthesia to pain, temperature, pressure, etc., over the distribution of all the branches of the fifth nerve. Hearing is not impaired on the left side. The left pupil is active to light and accommodation. Tearing is about the same in both eyes. There is more or less complete anosmia on the left. Taste to salt, acid, sugar and quinine is markedly diminished on the left, both on the soft palate and the tongue. Gag reflex is absent on the left, present on the right. Pain and temperature sensations are absent on the left half of the tongue.

"Mrs. B. appears to me to be much improved. But she still complains of a constant, dull pain in the region of the left zygoma. This pain radiates to the left parietal region. She complains of parathesias, such as prickling sensation along the lower jaw. She states that at times this same sensation is present over the left eye and rarely over the rest of the distribution of the fifth nerve. Also, the left eye appears considerably deeper in the orbit than the right, and there is slight drooping of the upper lid. She still has a great deal of difficulty in swallowing anything but liquids, and she states even liquids cause severe pain. She is unable to chew any solid food so she confines herself to liquids and mushy solids. However, she has gained four pounds in weight in the last five weeks. She also complains of a severe photophobia in the left eye. This does not start the pain in the zygoma as it used to. The severe jumping pain that was the worst of all has been absent since our resection of the sphenopalatine ganglion. She is now able to sleep as much as six hours at a time if she takes two or three three-grain capsules of sodium amytal. Up to five weeks ago she used half a grain of morphin as well as two sodium amytals to get three hours' rest. She has had no morphin for five weeks.

The following communication has since been received from the attending physician:

"I have not seen Mrs. B. for quite some time. When I last saw her she was about as miserable as ever. She still complains of a constant pain over the distribution of the left fifth nerve. The pain is almost always present, but is worse at some times than at others. There seems to be no relation to temperature or time with the exacerbations. She takes large quantities of sodium amytal but for the last several weeks has not required opiates. She did require large doses of opiates for several months since her operation. She went without opiates for three months or more immediately following resection of the ganglion. The severe, jumping pain of which she complained before the resection of the ganglion has never returned. She has had two neurologists go over her since her last visit here and has had a course of x-ray therapy with far less resultant benefit than from our operation.

"I am now firmly convinced that her pain is of central origin, as every sensory or possibly sensory nerve on the left side has now been cut and she still has her pain. Incidentally, she has lost no weight and looks as well as she ever did since her first visit to my office."

STANFORD UNIVERSITY HOSPITAL.

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THYROID PARAGANGLIOMA

RICHARD E. BROWNLEE, MD
PORTLAND, OREGON

WILLIAM W. SHOCKLEY, MD
CHAPEL HILL, NORTH CAROLINA

Paraganglioma of the thyroid gland is a rare neoplasm. Only eight cases have previously been reported. The neoplasm was confined to the thyroid in all but two patients; laryngeal involvement was seen in one and tracheal involvement in another. A review of these previously reported cases is presented along with the details of an additional case with laryngeal involvement. Laryngeal and thyroid paragangliomas are compared and contrasted. The anatomic and embryologic basis of these tumors and the diagnosis and treatment are discussed. We suggest changing the nomenclature and reporting of these lesions on the basis of their apparent common origin. Surgery remains the treatment of choice in most paragangliomas, including those involving the larynx and thyroid. Although the number of reported cases is small, there have been no cases of distant metastases or local recurrence after adequate surgical removal.

KEY WORDS — chemodectoma, glomus tumor, laryngeal neoplasm, laryngeal paraganglioma, thyroid neoplasm, thyroid paraganglioma.

INTRODUCTION

Paragangliomas of the head and neck region are rather uncommon tumors; however, they have been reported with increasing frequency in recent years. This increase appears to be due to heightened awareness of this neuroendocrine lesion and the inclusion of paraganglioma in the differential diagnosis of masses in this region. Most paragangliomas (also called chemodectomas, chromaffinomas, and glomus tumors) are related to the arteries and nerves of the branchial arches, with the most common being carotid body, jugulotympanic, intravagal, laryngeal, and nasal-nasopharyngeal.[1]

The paraganglionic system was discovered over 200 years ago with the description of the carotid body by von Haller in 1743.[2,3] In 1904 the carotid body and carotid body–like tissue were integrated with the adrenal medulla into one system, the paraganglia.[4] Paraganglia are extra-adrenal collections of neural crest cells that can be separated into related groups based on anatomic, histologic, and histochemical parameters. These groups include branchiomeric, intravagal, aorticosympathetic, and visceral-autonomic groups, with most in the head and neck being of branchiomeric origin.[1]

The first reported thyroid paraganglioma was described by Haegert et al[5] in 1974. Since that time seven other paragangliomas of thyroid origin have been reported. The neoplasm was confined to the thyroid in all but two patients: laryngeal involvement was seen in one and tracheal involvement in another.[6-12] A review of these previously reported cases is presented along with the details of an additional case with laryngeal involvement.

CASE REPORT

A 27-year-old woman was evaluated by a local surgeon for a 1- to 2-year history of an asymptomatic mass in the right lobe of the thyroid. There was no family history of thyroid disease, no history of irradiation of this area, and no clinical or laboratory evidence of hypothyroidism or hyperthyroidism. Shortly thereafter she underwent a right thyroid lobectomy, at which time residual tumor was left on the right recurrent laryngeal nerve and tracheoesophageal groove. At this point, she was referred to the University of North Carolina Hospitals for further evaluation and treatment. The original pathologic diagnosis was medullary carcinoma. Postoperatively she experienced hoarseness from a right vocal cord paralysis, which quickly resolved. Review of the surgical specimen revealed a *Zellballen* pattern by light microscopy and immunohistochemical stains positive for S-100 and chromogranin and negative for thyroglobulin and calcitonin (Fig 1). These findings led to the diagnosis of paraganglioma of the thyroid gland.

Physical examination revealed a healing thyroidectomy scar and a violaceous submucosal mass in the region just inferior to the right true vocal cord. Vocal cord function at this time was normal and no other abnormalities were seen at videostroboscopy. A previously obtained bone scan and chest radiograph were normal. Magnetic resonance imaging (MRI) and polytomography showed a 1 x 1.5-cm lesion encompassing the cricoid cartilage and first tracheal ring (Figs 2 and 3). The patient was taken to the operating room, where the tumor was excised under direct vision via a laryngofissure. The resection involved removing the right subglottic larynx (including the overlying thyroid cartilage), the right half of the cricoid (preserving the cricoarytenoid joint), the first tracheal ring, and the right recurrent laryngeal nerve. The area was reconstructed

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From the Division of Otolaryngology–Head and Neck Surgery, University of North Carolina–Chapel Hill, Chapel Hill, North Carolina. Dr Brownlee is currently in the Department of Otolaryngology–Head and Neck Surgery, Oregon Health Sciences University, Portland, Oregon.

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REPRINTS — William W. Shockley, MD, 610 Burnett-Womack Bldg, CB 7070, Division of Otolaryngology–Head and Neck Surgery, University of North Carolina–Chapel Hill, Chapel Hill, NC 27599-7070.

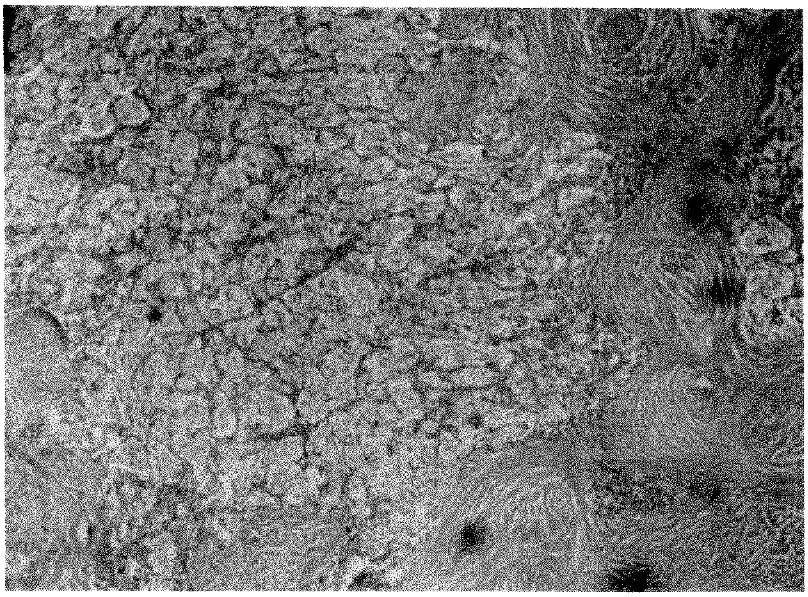

Fig 1. Photomicrograph shows epithelial cell nests surrounded by vascular connective tissue stroma: *Zellballen* pattern.

with a cartilage rib graft placed laterally and an auricular cartilage graft to cover the remaining defect anteriorly. An Aboulker stent wired to a metal tracheostomy tube was placed so as to stent open the reconstructed subglottis.

Examination of the surgical specimen showed all margins of resection to be free of tumor and confirmed the previous diagnosis of thyroid paraganglioma (Fig 4). The Aboulker stent was removed 6 weeks postoperatively and the patient has done well except for a moderate amount of granulation tissue, which was removed with a carbon dioxide laser. Her voice, originally weak, has improved with a vocal cord medialization procedure (Isshiki thyroplasty type I). A repeat MRI scan 7 months after resection revealed no evidence of recurrent tumor. Eighteen months postoperatively, the patient continues to return for follow-up with no evidence of recurrent disease.

DISCUSSION

There have been eight previously reported cases of thyroid paraganglioma.[1,5-11] However, the true incidence of these tumors is hard to establish, as they may have previously been misdiagnosed as medullary thyroid carcinomas, carcinoid tumors, atypical adenomas, etc.[13]

Multiple anatomic studies have confirmed the presence of the symmetrically located pairs of superior and inferior laryngeal paraganglia.[2,9,12,14] The smaller, relatively constant superior group is related to the internal branch of the external laryngeal nerve and are found in the upper, anterior third of the ventricular fold near the superior edge of the thyroid cartilage.[2,12,14] The inferior paraganglia are larger and less constant in location. They are most often located between the cricoid cartilage and first tracheal ring, but may be positioned more laterally. The inferior glands are also described as being in contact with the thyroid gland or spread over or within its capsule.[2,12] This location could explain the origin of thyroid paragangliomas.

Presentation and History. The collected series of patients consists of nine women 9 to 73 years of age with a mean age of 42 years (see Table[1-8]). There have been no documented cases of thyroid paragangliomas in men. This is in contrast with laryngeal paragangliomas, for which the female to male ratio is approximately 1:1.[3,4,15] A review of 69 patients with paragangliomas of the head and neck region by Lack et al[16] in 1977 showed a female predominance in groups with vagal body tumors (female to male ratio of 11:2) and jugulotympanic tumors (7:1), but the most common type, carotid body tumors, showed no sex predilection (22:21).

All patients with thyroid paragangliomas have presented with a mass in the neck, and most lack symptoms referable to the larynx. Other symptoms included hoarseness (two of nine or 22%), pain (two of nine), hemoptysis (one of nine or 11%), and stridor (one of nine). Dysphagia was not reported in any patients. In most cases the duration of symptoms prior to diagnosis was not given, and therefore it is hard to know whether these tumors have a prolonged natural history as is reported with laryngeal paragangliomas.[4] No patients had a history of prior head and neck irradiation.

The lesion was predominantly left-sided in four of nine cases (44%), right-sided in two of nine (22%), in the midline or isthmus in two of nine (22%), and was not specified in the remaining case. The numbers are too small to draw any significant conclusions about the laterality of these lesions. Reports of head and neck paragangliomas have stressed the familial tendency of these lesions and their association with other benign and malignant tumors; whether the same will be true of thyroid paragan-

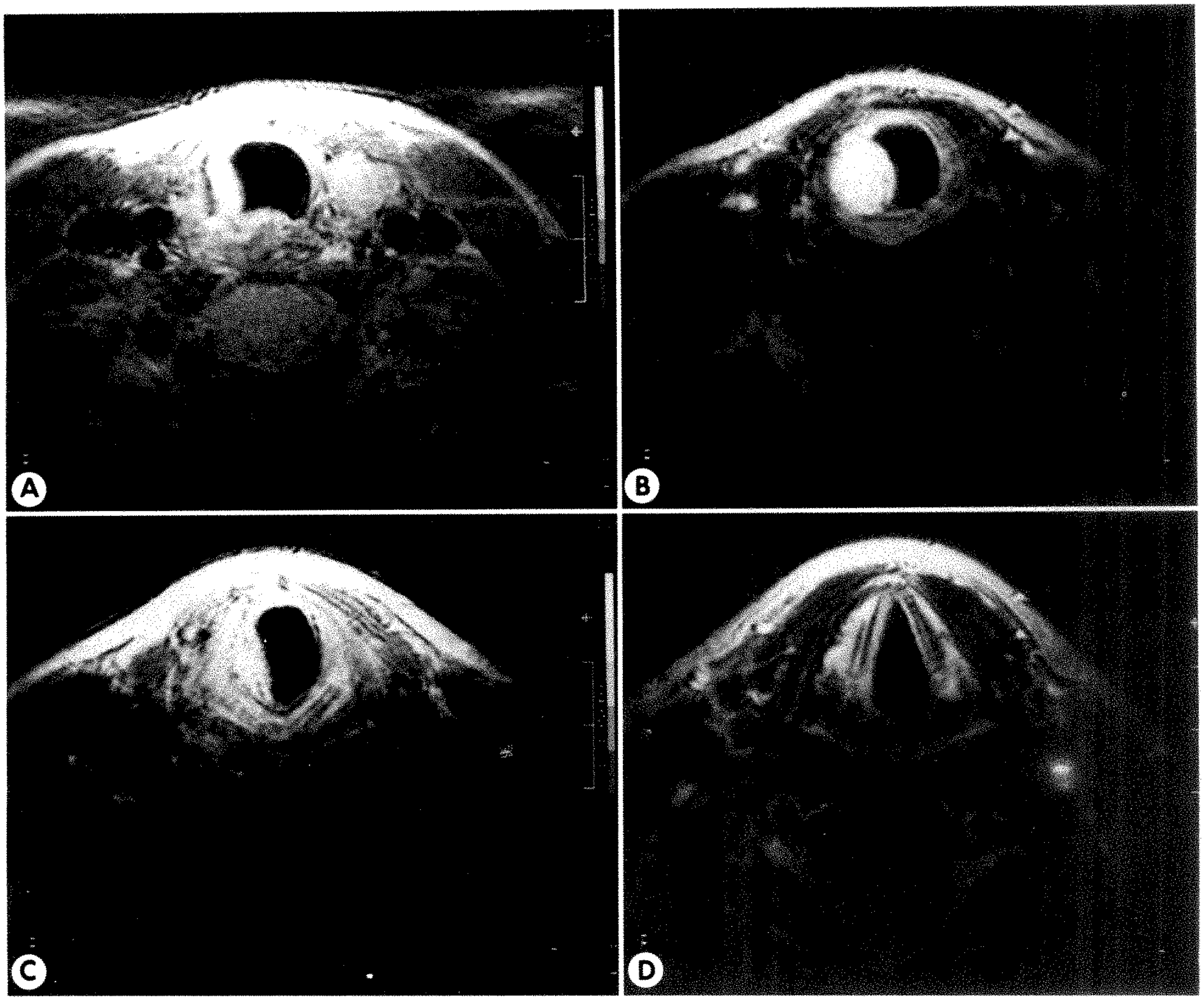

Fig 2. T2-weighted magnetic resonance images showing 1.5-cm lesion at level of cricoid cartilage and first tracheal ring. A) Tumor involving first tracheal ring. Note intact left thyroid lobe. B) Involvement of cricoid ring. C) Tumor extension into conus elasticus. D) Vocalis muscle is not involved.

gliomas remains to be seen.[16,17] One patient with a thyroid paraganglioma showed evidence of multicentric disease; the thyroid lesion was associated with bilateral carotid body tumors.[5] Other paragangliomas of the head and neck have a reported 10% incidence of multicentricity.[16,17] There were no bilateral thyroid tumors; this appears to be the same trend as with laryngeal lesions.[4] The highest incidence of bilateral paragangliomas is 26% in familial carotid body tumors, while only 3% of the nonfamilial type are bilateral.[17]

Diagnosis. The diagnosis of thyroid paraganglioma follows many of the same principles involved in evaluating any neck or thyroid mass. One of the most important factors is being aware of the lesions and including them in the differential diagnosis of masses in this location. A thorough physical examination including indirect laryngoscopy should be performed on all patients. The findings of a neck mass associated with a violaceous, submucosal, subglottic lesion would be consistent with the diagnosis of thyroid or inferior laryngeal paraganglioma. The neck should always be palpated for evidence of regional spread.

The ability of fine-needle aspiration to make the diagnosis of either thyroid or laryngeal paraganglioma has not been reported. Fine-needle aspirates from other paragangliomas, such as those associated with the carotid body and vagal body, confirm the diagnosis in about 50% of cases.[16]

Angiography, which is considered important in the diagnosis, workup, and preoperative preparation of other head and neck paragangliomas, is not essential in the evaluation of the thyroid or laryngeal variety.[3,15-17] For other paragangliomas, selective angiography can be used to detect synchronous lesions, demonstrate the blood supply to the tumor, or perform preoperative embolization.[3] However, since there are few synchronous lesions reported and the blood supply from the thyrocervical trunk is constant and easily controlled, the risks of angiography

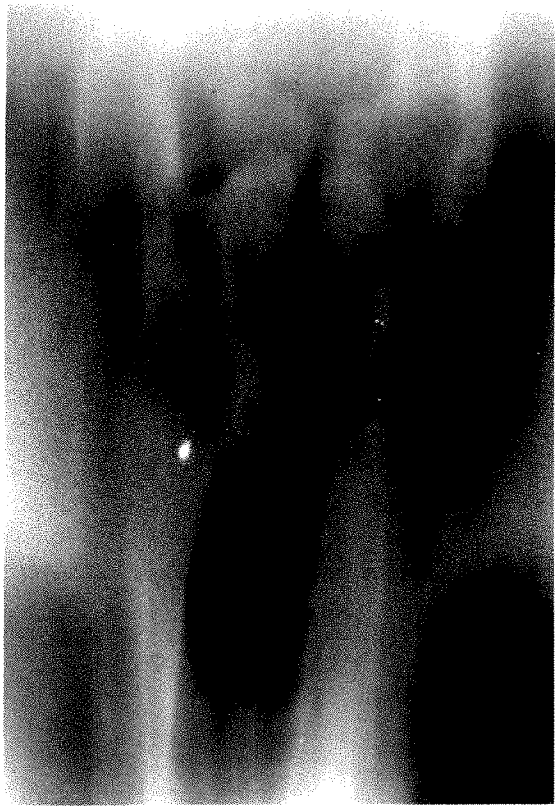

Fig 3. Polytomograph accurately outlining lesion, showing intraluminal involvement of right subglottic larynx.

do not appear to be warranted in the evaluation of thyroid paragangliomas. Thyroid scans also do not appear to be useful. The results of thyroid scans have been reported in five of nine (55%) patients; a cold nodule was seen in four of five (80%) scans, while the findings on the other scan were described as normal. No hot nodules were reported. This result is not surprising, as cold thyroid nodules are indicative of cyst formation, degenerative changes (such as hemorrhage, edema, calcification, or fibrosis), thyroiditis, or neoplasm. We do not feel that thyroid scans add any information that will help determine the management of patients with thyroid paragangliomas, and therefore do not recommend them as part of the workup of these tumors.

A computed tomography scan or MRI scan should be obtained if this type of tumor is suspected. These can add information such as laryngotracheal involvement or evidence of neck metastasis, both of which would affect therapeutic options. Another useful but often overlooked diagnostic study is polytomography. Tomograms accurately outlined the extent of subglottic involvement in our patient (Fig 3).

Histology. The typical histologic pattern of all paragangliomas is characterized by distinct clusters of chief cells surrounded by a prominent fibrovascular and reticulin stroma of sustentacular cells forming a characteristic *Zellballen* apearance (Fig 1). The chief cells contain 100- to 200-μm, electron-dense, membrane-bound cytoplasmic granules characteristic of neurosecretory granules.[14]

Marked nuclear pleomorphism, increased mitotic activity, hyperchromatism, and local invasion, the usual accepted criteria for malignancy, do not correlate with the incidence of metastasis or the ultimate biologic behavior of paragangliomas.[18-21] In fact, invasion of local structures such as the larynx or trachea does not necessarily indicate malignancy as it does with other types of thyroid neoplasms. Malignancy can only be determined by regional or systemic metastasis, most commonly to regional lymph nodes, lung, and bone.[3,16] With such a small number of cases the true incidence of malignancy is difficult to determine, but so far there have been no reports of regional or systemic metastasis with thyroid paraganglioma. No local recurrences were seen in the seven cases in which follow-up was given. The length of follow-up ranged from 9 months to 7

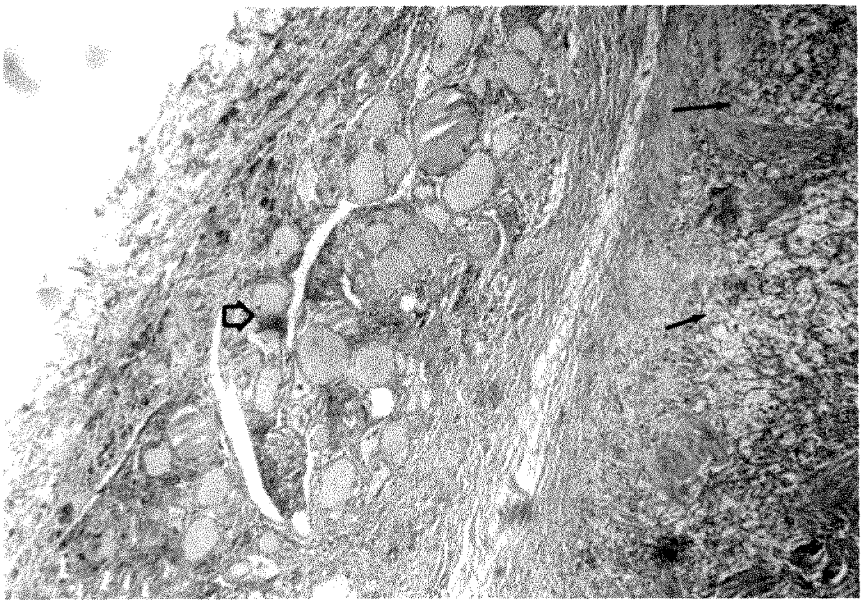

Fig 4. Photomicrograph showing both normal thyroid tissue (open arrow) and adjacent paraganglioma (closed arrows).

REPORTED CASES OF PARAGANGLIOMA

Reference	*Age*	*Sex*	*Side*	*Laryngeal Involvement*	*Thyroid Scan*	*Recurrence*	*Follow-up*	*Surgery*	*Other Paragangliomas*
1	44	F	L	Cricotracheal space	No	No	7 y	Total laryngectomy	None
2	36	F	L	No	Cold	No	5 y	L thyroid lobectomy	Yes*
3	50	F	R	Anterior trachea	Cold	No	2 y	Total thyroidectomy, resection of anterior trachea	None
4	9	F	?	No	No	?	?	Subtotal thyroidectomy	None
5	50	F	L	No	Cold	No	3 y	L thyroid lobectomy	None
6	73	F	L	No	No	No	2 y	L thyroid lobectomy	None
7	36	F	I	No	No	No	?	Excision of nodule	None
8	50	F	I	No	Normal	No	9 mo	Excision of nodule	None
This report	27	F	R	Cricoid cartilage	No	No	18 mo	R thyroid lobectomy, resection of R subglottic larynx	None

L — left, R — right, I — isthmus.

*Patient with synchronous bilateral paragangliomas at carotid bifurcations.

years, with the average being 3 years (see Table).

Opinions differ concerning the malignant potential of laryngeal paragangliomas. Smith et al[4] believe that these laryngeal lesions exhibit a higher rate of malignancy than paragangliomas at other sites. Using the previously stated criteria for malignancy, their review of the 52 reported cases found evidence of malignancy in 25%. Others believe the incidence to be overestimated; that these lesions are generally benign, with little tendency to metastasize; and that reported malignant paragangliomas are often misdiagnosed carcinomas.[18,22] Pheochromocytomas and other extra-adrenal paragangliomas are malignant in approximately 10% of cases.[3,15,16]

Etiology and Comparison With Inferior Laryngeal Paraganglioma. Review of the literature on laryngeal and thyroid paraganglioma suggests that several of these lesions could be described as originating from either location, depending on one's interpretation of the reports. One of the cases we have included[1] has also been included in reviews of laryngeal paragangliomas.[4] We have included this case in our report because we feel that it likely represents a thyroid lesion with laryngeal involvement. According to Olofsson et al, "The patient was a 44-year-old woman who was found to have a dumbbell-shaped lesion with the largest portion in the left lobe of the thyroid gland."[1(p57)]

The largest review of laryngeal lesions (which included Olofsson's patient) described only 4 cases out of 52 as being subglottic or of inferior paraganglia origin.[4] Most laryngeal paragangliomas are supraglottic (from the superior ganglia) and are described as being lesions that "tend to remain unilateral with limited extralaryngeal extension."[3(p47)] The mean age at presentation with these laryngeal tumors is 49 years, and there is an equal male to female distribution.[4] Most patients present with symptoms referable to the larynx; hoarseness is the most common complaint and is reported in 70% of the cases. Laryngeal paragangliomas have a prolonged natural history, with the mean duration of symptoms being 47 months. Physical examination reveals a submucosal, erythematous mass, with the most common site being the aryepiglottic fold, followed by the false vocal cord.[3,4,18]

As previously noted, there have been only four subglottic (inferior laryngeal) paragangliomas reported. The patient with the dumbbell-shaped lesion reported by Olofsson et al[1] has been described above. Martinson alludes to two other patients: one a 14-year-old boy with a "glomus laryngicum inferior,"[23(p70)] and another case related to the author via a personal communication.[23] No specifics of the latter case are reported. In a review of "chemodectomas," Ani et al[24] report a case involving the right subglottic region of a male whose age is not specified. They state that there was a paralysis of the vocal cord due to the tumor's being "around the end of the recurrent laryngeal nerve."[24(p45)]

Although the number of reported inferior laryngeal paragangliomas is small, they appear to be very similar to the thyroid paragangliomas described. Similarity is difficult to ascertain when dealing only with the case reports and not the actual pathologic material, but their presentation and clinical course are almost identical. Laryngeal "involvement," as reported with thyroid paraganglioma, may be more a manifestation of the site of origin of the lesion than a reflection of its biologic behavior. Anatomic studies have shown that the inferior laryngeal paraganglia can be found in various locations — most commonly between the cricoid cartilage and the first tracheal ring. These inferior paraganglia can also be seen between the inferior horn of the thyroid cartilage and the cricoid carti-

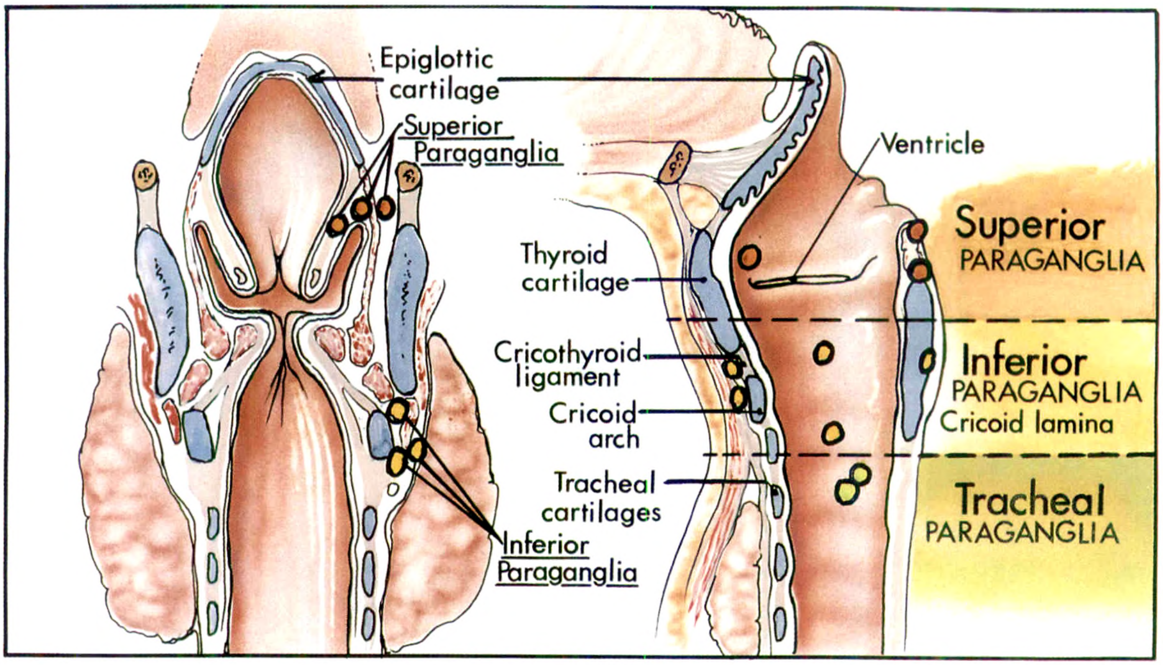

Fig 5. Diagram of laryngeal paraganglia. Lateralmost inferior paraganglia lie adjacent to thyroid gland. (Modified from Lawson and Zak.[2])

tilage in close relationship to the inferior thyroid artery and recurrent laryngeal nerve, and may extend to or arise within the capsule of the thyroid gland (Fig 5).[2,12]

We believe the inferior laryngeal paraganglia are the origin of both inferior laryngeal and thyroid paragangliomas and therefore that these lesions are different presentations of the same clinical entity. Lawson and Zak state, "The point of origin of the tumor from a submucosal body or one situated more laterally will determine whether the neoplasm will present as an intraluminal, lateral cervical, or dumbbell-shaped mass."[2(p106)] Lesions that manifest as subglottic intraluminal masses have been labeled as inferior laryngeal tumors, and the lateral cervical lesions as thyroid paraganglioma. The dumbbell-shaped tumors have been included in reports of both types; these are described as showing laryngeal invasion when they are thought to be of thyroid origin. The fact that "laryngeal invasion" has had no impact on recurrence or survival would also support this theory. Even though we have reported our case as a thyroid paraganglioma with laryngeal involvement, we suggest that all of these thyroid and inferior laryngeal tumors should be called inferior laryngeal paragangliomas, as this term most accurately reflects the origin of the lesions.

A more important distinction to make may be between the superior and inferior laryngeal varieties. As was previously discussed, the reported incidence of malignancy with laryngeal paraganglioma is as high as 25%. If this increased incidence is accurate, this may indicate a different biologic behavior of the superior and inferior neoplasms. This rate of malignancy is calculated from series that are heavily, if not totally, weighted toward superior laryngeal tumors.[4] In contrast, there have been no malignant inferior laryngeal lesions (including all previously reported thyroid and inferior laryngeal lesions). There also appears to be a difference in the sex incidence; the superior type have a female to male incidence of 1:1, whereas the inferior ones show a heavy female predominance (5:1).[1]

Treatment. Primary surgical excision remains the preferred method of treatment. Even though no cases of malignancy have been reported, these tumors should be approached with the assumption that they have malignant potential. Surgical approaches will differ depending on the exact location of the tumor, but an external approach will be required. If the larynx is involved, a laryngofissure, pharyngotomy, or partial laryngectomy will be required for excision, as an endoscopic approach will not be adequate. Elective neck dissection is not indicated in the treatment of these lesions. Since all reported cases of thyroid paraganglioma were treated surgically, the role for primary irradiation or chemotherapy remains undefined. It is difficult to make recommendations regarding irradiation or chemotherapy based on the experience with superior laryngeal lesions, as these modalities were only used in malignant and recurrent tumors.[4]

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7TH WORLD CONGRESS FOR BRONCHOLOGY & BRONCHOESOPHAGOLOGY

The 7th World Congresses for Broncology & Bronchoesophagology will be held Sept 28-Oct 2, 1992, at the Mayo Clinic and Mayo Medical Center in Rochester, Minnesota. For further information, contact Udaya B. S. Prakash, MD, Secretary-General & Director, 7th WCB & WCBE, East-18, Mayo Clinic, Rochester, MN 55905.

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PEDIATRIC TRACHEOBRONCHOMALACIA AND MAJOR AIRWAY COLLAPSE

CPT ERIC A. MAIR, MC, USAF
COL DAVID S. PARSONS, MC, USAF
LACKLAND AIR FORCE BASE, TEXAS

Based on histopathologic, endoscopic, and clinical findings of the flaccid airway, new descriptive terms — major airway collapse types 1 through 3 — are proposed to better define tracheobronchomalacia. A typing and grading system is offered to objectively analyze and compare clinical cases. Endoscopic and anesthetic techniques are presented for use in children with respiratory distress suggestive of tracheobronchomalacia. Spontaneous ventilation with laryngoscopic insufflation of anesthetic gases and the use of small-diameter telescopes without bronchoscopes are key elements for the examination of the dynamic pediatric airway. Pitfalls of classic bronchoscopy techniques are described that can lead to a missed diagnosis. Between 1987 and 1990, over 200 telescopic bronchoscopies were performed at Wilford Hall US Air Force Medical Center on 129 children 3 years old and younger with respiratory distress. By means of the described techniques, 38 children (30%) with major airway collapse were identified. Major airway collapse was associated with a variety of endoscopic and cardiac abnormalities. With the emergence of sophisticated neonatal pediatric respiratory care, a growing number of premature infants with major airway collapse are surviving. Early, precise endoscopic diagnosis allows optimal management.

KEY WORDS — bronchoscopy, endoscopy, major airway collapse, tracheobronchomalacia.

INTRODUCTION

Tracheobronchomalacia (TBM) is a flaccidity of the airway with weakening of the supporting tracheobronchial cartilaginous arches and widening of the posterior membranous wall. The airway collapses easily, causing the lumen size to diminish during expiration. Various degrees of obstruction result.

Although TBM is not a new topic, there exists confusion in the literature regarding its cause and the methods for diagnosis in children. Gross and Neuhauser[1] described pediatric TBM in 1948 and ascribed its cause to vascular compression. The following year, Evans[2] advocated radiography as the best method of diagnosis for TBM. Other authors have since supported this method of evaluation.[3-5] In 1952, Holinger et al[6] described the disorder as a partial or total collapse of the lumen on full expiration; the symptoms disappeared on passage of a rigid bronchoscope through the malacic segment. A decade later, Baxter and Dunbar[3] described TBM as a weakness of the large airway's wall due to softening of the cartilage with hypotonia of the myoelastic elements. They felt this was an isolated, self-limiting finding that would resolve within 2 years. In 1969, Mustard et al[7] stated that most cases of TBM were secondary to intrinsic tracheal softening, with less than 10% due to vascular compression. Benjamin et al[8] observed in 1976 that endoscopy was the most reliable diagnostic study and noted an association with other congenital anomalies. They further observed that TBM symptoms persisted beyond childhood. In 1986, Greenholz et al[9] reviewed the care of 41 infants treated for TBM and noted that specific management guidelines were lacking and surgical results were unsatisfactory.

Such confusion exists in part because there are no objective, reproducible, or concise diagnostic criteria for TBM. In this paper, we present anatomic, histologic, and embryologic parameters that allow objective typing and staging of this disorder. Endoscopic evaluation techniques are stressed that optimize a dynamic examination of the pediatric tracheobronchial tree.

Although other authors believe TBM to be a rare entity,[10-12] this study suggests the contrary. As Gupta et al[13] pointed out more than 20 years ago, the apparent rarity of TBM may simply be the failure to suspect it.

MATERIAL AND METHODS

From July 1987 to July 1990, over 200 rigid bronchoscopies with telescopes were performed on 129 children 3 years old and younger with acute or chronic respiratory distress by the Wilford Hall US Air Force Medical Center (WHMC) pediatric otolaryngology service. Owing to the nature of the military

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From the Department of Otolaryngology–Head and Neck Surgery, Wilford Hall US Air Force Medical Center, Lackland Air Force Base, Texas. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Air Force or the Department of Defense.

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REPRINTS — CPT Eric A. Mair, MC, USAF, Dept of Otolaryngology–Head and Neck Surgery, Wilford Hall USAF Medical Center, Lackland Air Force Base, TX 78236-5300.

referral system, children are flown to WHMC from all over the world. Infants and children were examined under general anesthesia, with spontaneous ventilation and laryngoscopic insufflation of anesthetic gases the preferred technique. Video and 35-mm slide photographic documentation was used when possible. Children were assessed for TBM on the basis of endoscopic criteria, with assistance from radiographic studies when indicated.

RESULTS

Thirty-eight infants and toddlers 3 years old and younger were found to have TBM (see Table). This represents 30% of 129 children of this age who underwent bronchoscopy for respiratory distress at WHMC during the 3-year period. Twenty-nine (76%) were boys and nine (24%) were girls.

Signs and symptoms of TBM varied and included acute or chronic respiratory obstruction with prolonged expiration, cyanosis, barking cough, stridor, apnea, difficulty feeding, and retained secretions with recurrent pneumonia.

Onset of symptoms occurred at birth in all but two children, whose symptoms began at 1 week of age. The deaths of seven infants in this series were due in part to respiratory obstruction from severe TBM. Thirteen (34%) affected children were premature, with gestational ages under 35 weeks. None of the patients had a family history of similar symptoms.[14] The delay from onset of symptoms to endoscopic diagnosis ranged from 1 day to 144 weeks, with a mean of 37 weeks. As the presenting symptoms of TBM became more commonly recognized by the pediatric staff, especially in premature infants with pulmonary immaturity, the delay to endoscopic diagnosis was shortened and the need for a better-defined typing system was recognized.

Associated anomalies were common. Twenty-two patients (58%) had cardiovascular abnormalities, including patent ductus arteriosus, ventricular or atrial septal defects, double aortic arch, tetralogy of Fallot, right ventricular hypertrophy, pulmonary valve stenosis, and others. Ten (26%) children had severe developmental delay. Associated endoscopic anomalies were noted in 24 (63%) children and included gastroesophageal reflux (12), subglottic stenosis (9), esophageal atresia (5), tracheal bronchus (4), true vocal cord paralysis (4), tracheoesophageal fistula (4), tracheal stenosis (2), and others. Laryngomalacia was not associated with TBM in our series.

The severity of TBM varied from mild to incompatible with life. Six infants had severe TBM associated with reflex apnea. Four of these six infants died of their disease. There was no association between location within the airway and severity. All four cases of TBM associated with a tracheal bronchus had the malacia below the aberrant bronchus. Other anomalies were not associated with the location of the malacia.

Twenty-six (68%) children had various degrees of bronchomalacia. Left main stem bronchomalacia was predominant in 16 (62%), 5 (19%) had mainly right main stem disease, and 5 (19%) had equal bilateral main stem bronchomalacia. No malacia was noted in the lower airways beyond the segmental bronchi.

Twenty (53%) children with TBM required tracheotomies. These were performed primarily to treat the associated anomalies (eg, subglottic stenosis, prolonged ventilator dependence). In only 3 of these 20 children was the tracheotomy performed to stent the trachea as a definitive mode of therapy. One child had Larsen's syndrome and died of extensive tracheal and bronchial involvement. Another had a double aortic arch repair but failed aortopexy. The third child had severe TBM with improvement noted only after placement of an endobronchial stent in conjunction with an elongated tracheotomy tube. In contrast, only 17 (13%) of the children without TBM required a tracheotomy.

DISCUSSION

Tracheobronchomalacia is characterized by expiratory airway collapse and may be exacerbated by any activity that induces an increased respiratory effort, such as crying, feeding, or coughing. Common clinical findings include stridor, barking cough, prolonged expiratory phase, and the "bagpipe sign" — an expiratory sibilant note persisting after the end of visible expiration.[15] Tracheobronchomalacia may lead to trapping of air and secretions, recurrent pneumonia, hypercarbia, progressive hypoxia with cyanosis, bradycardia, or reflex apnea that can result in cardiopulmonary arrest. Major airway collapse is the main factor linking these presenting signs and symptoms.

Pathologically, Wailoo and Emery[16] characterized tracheomalacia as the presence of tracheal cartilage that was reduced in length and had a widened posterior membranous wall and a greatly reduced anterior-posterior dimension. These findings were surmised from an extensive postmortem histologic study of 53 infants with tracheomalacia and tracheoesophageal fistula.[16] The ratio of anterior tracheal cartilaginous wall to posterior membranous wall in normal children is 4.5 to 1. This ratio becomes altered in children with tracheomalacia and may deform to 2 to 1. In an additional study of membranous tracheal walls of

PEDIATRIC TRACHEOBRONCHOMALACIA

Patient	*Sex*	*Gestational Age*	*Signs and Symptoms*	*Age at Onset*	*Age at Endoscopic Diagnosis*	*Tracheomalacia*	*Bronchomalacia*
1	M	Term	Reflex apnea, stridor, cyanosis, respiratory obstruction, difficulty breathing while eating	Birth	1 wk	Severe, cervical, middle, and distal	Severe L (greater than R) main stem
2	M	32 wk	Respiratory distress, failure to thrive, recurrent croup, recurrent pneumonia	Birth	20 mo	Moderate cervical and middle	Mild L and R main stem
3	F	Term	Transient tachypnea	Birth	13 d	Mild cervical and middle	Mild L main stem
4	F	34 wk	Respiratory distress and obstruction, ventilator dependence	1 wk	7 mo	None	Severe L main stem
5	M	34 wk	Respiratory obstruction, stridor	Birth	2 mo	Severe middle and distal	Mild L and R main stem
6	M	27 wk	Respiratory distress and obstruction	Birth	5 mo	None	Mild L main stem
7	M	36 wk	Respiratory distress and obstruction	Birth	5 mo	Mild middle and distal	Mild L and R main stem
8	M	Term	Cyanosis, prolonged expiration, stridor	Birth	10 mo	Mild distal	Mild L main stem
9	M	Term	Respiratory distress	Birth	21 mo	Moderate distal	Moderate R main stem; mild L main stem
10	M	Term	Respiratory distress	Birth	3 wk	Moderate middle and distal	Mild L and R main stem
11	M	27 wk	Respiratory distress	Birth	12 mo	Moderate middle and distal	None
12	F	25 wk	Respiratory distress and obstruction	Birth	18 mo	Moderate cervical	None
13	M	Term	Respiratory distress and obstruction, cyanosis	Birth	6 mo	Severe cervical, middle, and distal	None
14	M	Term	Respiratory distress and obstruction secondary to neck mass	Birth	6.5 mo	None	Moderate at R upper lobe takeoff
15	M	Term	Expiratory stridor, recurrent pneumonia	Birth	8 mo	None	Severe L main stem
16	F	26 wk	Respiratory distress and obstruction	Birth	22 mo	Moderate middle	None
17	M	41 wk	Respiratory distress and obstruction	Birth	6 wk	Severe middle and moderate cervical	None
18	M	Term	Recurrent croup, nocturnal respiratory distress, apnea	Birth	12 mo	Moderate distal	Moderate L (greater than R) main stem
19	M	Term	Respiratory distress and obstruction, cyanosis	Birth	1 d	Mild cervical and distal	Moderate R (greater than L) main stem
20	M	35 wk	Respiratory distress and obstruction	Birth	4 mo	Severe middle and distal	Mild L main stem
21	M	Term	Respiratory distress and obstruction, recurrent pneumonia, cyanosis	Birth	13 mo	Moderate middle and distal	Severe R main stem; mild L main stem
22	M	Term	Cyanosis, reflex apnea, respiratory distress and obstruction	Birth	1 wk	None	Severe L main stem
23	F	Term	Respiratory obstruction, reflex apnea	Birth	1 wk	Moderate cervical and distal	Severe L main stem
24	M	25 wk	Stridor, respiratory distress and obstruction	Birth	24 mo	Mild cervical	None
25	M	Term	Respiratory distress, cyanosis, reflex apnea	Birth	3 mo	Severe cervical and middle	Mild L main stem
26	M	Term	Stridor, postprandial cyanosis	Birth	12 mo	Mild cervical	None
27	M	36 wk	Recurrent pneumonia, respiratory obstruction	Birth	2.5 mo	Moderate cervical	None
28	F	Term	Respiratory distress and obstruction	Birth	15 mo	Mild cervical, middle, and distal	None
29	M	Term	Cyanosis, reflex apnea, respiratory distress and obstruction	Birth	16 mo	Severe middle and distal	Severe L main stem; mild R main stem
30	M	28 wk	Respiratory distress and dyspnea	Birth	36 mo	None	Severe distal R main stem at takeoff of R upper lobe
31	M	Term	Respiratory distress and obstruction	Birth	3 mo	Severe distal	Severe L main stem; mild R main stem
32	F	28 wk	Respiratory obstruction and distress, cyanosis	Birth	24 mo	Moderate middle	None
33	F	28 wk	Inspiratory and expiratory stridor	Birth	6 mo	Moderate to severe middle	None
34	M	Term	Stridor with agitation, persistent cough	1 wk	7 mo	Moderate distal	None
35	M	Term	Cyanosis, respiratory distress and obstruction, reflex apnea	Birth	1 mo	None	Severe L and R main stem
36	F	42 wk	Respiratory distress and obstruction	Birth	3 d	None	Mild L main stem
37	M	31 wk	Apnea, respiratory obstruction	Birth	11.5 mo	None	Severe L main stem
38	M	34 wk	Respiratory distress, apnea	Birth	6 mo	Moderate cervical, distal	Mild L (greater than R) main stem

PEDIATRIC TRACHEOBRONCHOMALACIA (Continued)

Tracheotomy	*Duration of Ventilatory Support*	*Associated Anomalies*	*Comments*
Yes	2.5 y	Pierre-Robin sequence, bilateral short femurs, tapes equinovarus, developmental delay	Elongated tracheotomy tube and self-expanding woven stent to L main stem bronchus
No	8 wk	Esophageal atresia without TEF, R TVC paralysis, GER, VSD, PDA	Colonic interposition graft
No	2 d	Esophageal atresia, TEF, GER, trisomy 18, VSD, PDA, ASD, jaundice, dysmorphism	Proximal pouch, distal TEF
No	6 mo	Tracheal bronchus, trisomy 21, PDA, pulmonary valve stenosis, VSD	Successfully extubated without evidence of subglottic stenosis
Yes	3 wk	Subglottic stenosis, R TVC paresis, congenital ascites, cryptorchidism, inguinal hernias, asplenia, nonimmune fetal hydrops	Respiratory obstruction exacerbated by large congenital ascites
Yes	158 d	BPD, hypothyroidism, ROP, seizure disorder, PDA, inguinal hernia	None
Yes	9 mo	Congenital cystic adenomatoid R lung malformation, widened carina, GER, seizures, optic nerve hypoplasia, cor pulmonale, developmental delay, ventriculomegaly, RAD, BPD, ROP	Died
No	None	Innominate artery compression	None
Yes	1 mo	Tracheal bronchus, subglottic stenosis, GER, craniosynostosis, hydrocephalus, developmental delay, R ventricular hypertrophy, ASD, anomalous pulmonary venous return, RAD, inguinal hernia, scoliosis, micrognathia, macroglossia, metatarsus varus, cryptorchidism	Tracheomalacia was below tracheal bronchus
No	35 d	Omphalocele, BPD, PDA, small thoracic-abdominal cavity	None
No	2 mo	Innominate artery compression, GER, PDA, seizures, RAD	None
Yes	2 mo	Subglottic stenosis, L TVC paralysis, GER, pulmonary valve stenosis, seizures, strabismus, PDA, ROP, BPD	Decannulated at 2.5 y, Nissen fundoplication
Yes	13 mo	Pulmonary atresia, ASD, R ventricular outflow tract obstruction	Died
No	1 mo	Large cervicomediastinal cystic hygroma	R neck dissection at 1 d of life
No	None	None	None
No	1 wk	Stenosis of lowest third of trachea, vesicoureteral reflux, scoliosis, rectal aplasia, rectovaginal fistula	Resection of stenotic segment with 1° anastomosis
No	None	Trisomy 21, long gap esophageal atresia, PDA	No TEF
No	5 d	Subglottic stenosis, developmental delay, trisomy 21, ASD, PDA, VSD	Prolonged endotracheal intubation
Yes	4 mo	Tracheal bronchus, GER, subglottic stenosis, esophageal atresia, TEF, craniosynostosis, absent corpus callosum	Underwent repair of TEF laryngotracheoplasty
Yes	4 mo	TEF without esophageal atresia, PDA, large VSD, GER, dysmorphism	Montgomery procedure to close vocal cords because of persistent aspiration, died
Yes	4 mo	GER, bilateral vertical tali, gray matter degenerative process, developmental delay, hypoplastic optic nerve, dysmorphism, neuromuscular abnormality	None
Yes	4 mo	Hypoplastic R ventricle, hypoplasia and atresia of pulmonary valve, tricuspid atresia, PDA, VSD	Self-expanding zigzag metal stent to L main stem bronchus, died
Yes	2 y	Tetralogy of Fallot, developmental delay	Prolonged continuous positive airway pressure
Yes	3 mo	Subglottic stenosis, paralyzed R TVC, subluxation of first tracheal ring, developmental delay, GER, BPD, ROP	Laryngotracheoplasty
Yes	12 d	Larsen's syndrome with joint laxity and hypotonia, developmental delay, pectus excavatum, RAD	Failed tracheopexy and extended tracheotomy tube, died
No	None	RAD	None
No	None	Esophageal atresia, GER	None
Yes	3.5 mo	Subglottic stenosis, mild tracheitis, BPD	None
Yes	17 mo	BPD, cryptorchidism, hypospadias, microcephaly, PDA, dysplastic valve, tetralogy of Fallot, complete pulmonary artery atresia, developmental delay, seizures, esotropia, cerebral atrophy, omphalocele, bilateral inguinal hernias, neuromuscular abnormality	Died
No	None	BPD	None
Yes	8 mo	Double aortic arch, PDA, congenital nystagmus	Ligation and division of L arch, requires elongated tracheotomy tube
Yes	30 mo	BPD, PDA, GER, R ventricular hypertrophy, cor pulmonale, developmental delay, ROP	Nissen fundoplication
No	7 d	Subglottic stenosis, BPD	One of triplets
No	None	Double aortic arch	Ligation and division of L arch
Yes	1 mo	Tracheal stenosis, severe congenital heart disease	Died
No	None	Congenital lobar emphysema, ASD, RAD	Endoscopy at 3 d of age with ball valve L main stem obstruction, repeat endoscopy at 3 y of age showed mild clinically insignificant bronchomalacia
No	3.5 wk	Tracheal bronchus, Hunter's syndrome, hypertelorism, RAD	None
Yes	2 wk	Subglottic stenosis	None

TEF — tracheoesophageal fistula, TVC — true vocal cord, GER — gastroesophageal reflux, PDA — patent ductus arteriosus, VSD — ventricular septal defect, ASD — atrial septal defect, BPD — bronchopulmonary dysplasia, ROP — retinitis of prematurity, RAD — reactive airway disease.

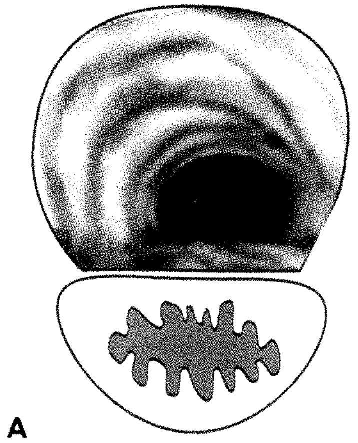
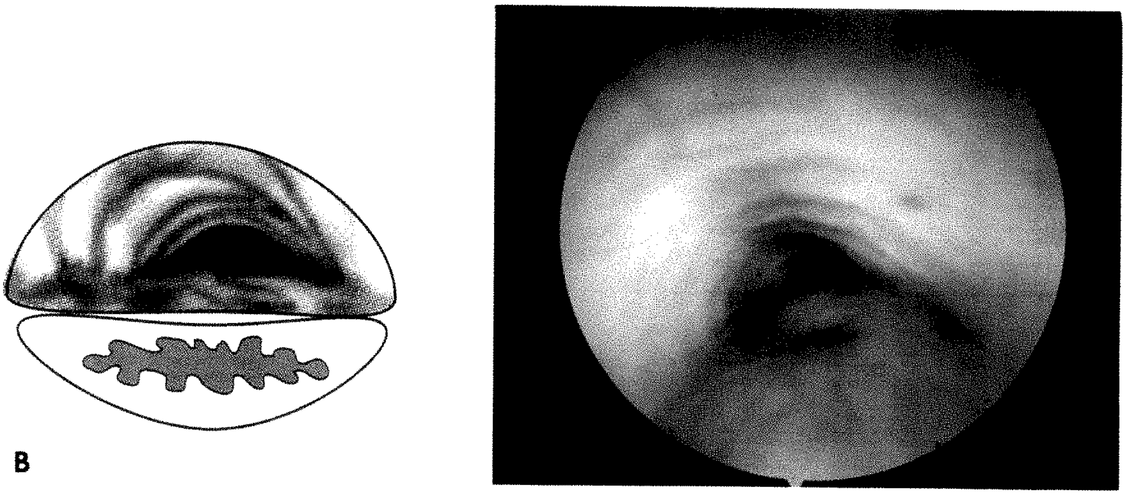


Fig 1. Schematics and endoscopic photographs of trachea. A) Normal trachea with ratio between cartilage and posterior membrane of approximately 4.5 to 1. B) Major airway collapse type 1. Cartilage to posterior membrane ratio approaching 2 to 1 is seen at birth. Type 1 is caused by intrinsic tracheal or bronchial abnormalities. We have found type 1 to be associated with esophageal atresia, tracheoesophageal fistula, mucopolysaccharidosis, and Larsen's syndrome. (Continued on next page.)



60 children, absence of the longitudinal muscle orrelated with intrathoracic tracheal collapse.[17] These hanges may be due to an embryologic mishap or cquired from chronic high airway pressures leading ɔ an enlarged collapsing airway.[18] The cause of the irway collapse remains unclear.

We have noted three distinct types of major airway ollapse (MAC; Fig 1). Type 1 is congenitally present ı infants or children and does not involve external irway compression. Baxter and Dunbar[3] referred to ıis as primary tracheomalacia and felt it was due to ıtrinsic tracheobronchial cartilage immaturity. Othrs postulated that the disorder was due to abnormal artilage composition.[19,20] No human histopatholog- : or histochemical studies have been performed to ubstantiate these theories. Type 1 is seen in some remature infants and has been identified in children ith associated congenital anomalies such as esophaeal atresia, tracheoesophageal fistula,[8] mucopolyıccharidosis,[20] and Larsen's syndrome.[21] It is unɔmmon for this type to be seen as an isolated finding ithout associated anomalies.

Major airway collapse type 2 is seen in infants or ıildren with abnormalities involving extrinsic tracheal and/or bronchial compression and, consequently, may be congenital or acquired; these include cardiovascular anomalies (eg, double aortic arch,[22] late takeoff of the innominate artery,[23] and left atrial hypertrophy[24]), bronchogenic cysts,[25] teratomas,[25] cystic hygromas,[25] hemangiomas,[25] pectus excavatum,[26] severe scoliosis,[27] thymus enlargement,[2] and goiter.[28] Type 2 is caused by extrinsic effects on previously normal airway cartilage, and the ratio of the arch to the posterior membranous wall may be unchanged at 4.5 to 1, despite the obvious deformity.

Major airway collapse type 3 is an acquired malacia arising from prolonged increased ventilatory airway pressures, from tracheotomy,[5] or from inflammatory processes causing severe tracheobronchitis.[5,29] Type 3, or acquired malacia, is initially progressive and has been seen to worsen over months, both clinically and endoscopically. In our experience, this has been seen most frequently in children with tracheotomies.

Types 1, 2, and 3 usually occur separately, but may be found in combination with each other. Both types 1 and 3 have a characteristic static endoscopic appearance with flattening of the cartilaginous arch and widening of the posterior membranous wall. This

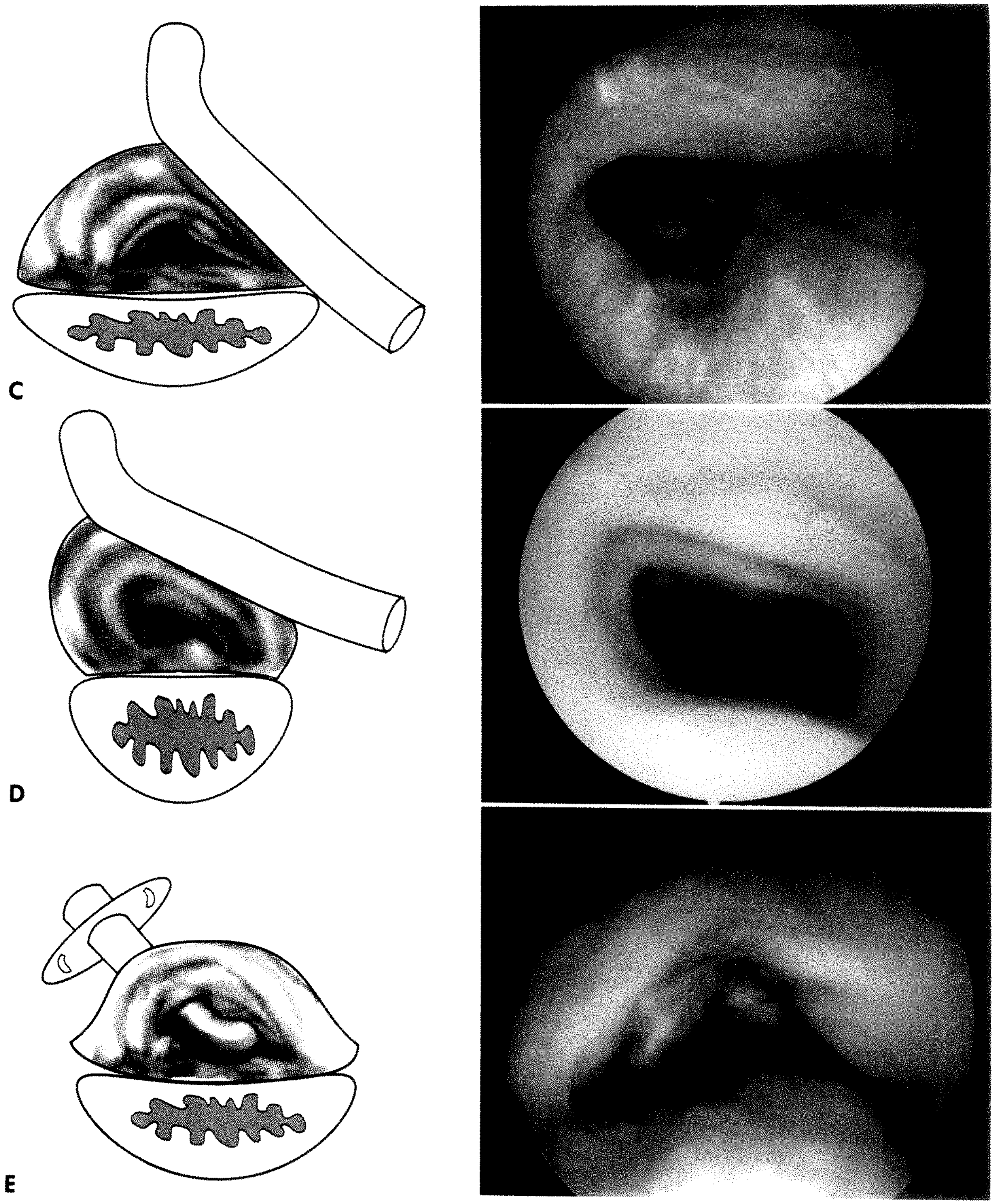


Fig 1, continued. C,D) Major airway collapse type 2. C) Cartilage to posterior membrane ratio approaching 2 to 1 is commonly seen. Type 2 is caused by extrinsic effects on previously normal airway cartilage and may be congenital or acquired. Causative factors include cardiovascular anomalies (eg, innominate artery compression, as shown here), bronchogenic cysts, and others. D) Major airway collapse type 2 without 2 to 1 ratio of cartilage to posterior membrane. Obvious deformity of airway is noted, yet ratio may remain normal in type 2. This form of type 2 is not as common as its malacic counterpart, shown in C. E) Major airway collapse type 3. This is acquired malacia with ratio of cartilage to posterior membrane approaching 2 to 1. This may be seen in infants and children with tracheotomies (shown here), prolonged increased ventilatory airway pressures, or severe inflammatory diseases.

often approaches a 2 to 1 ratio. The strength of the cartilaginous arch may be normal initially, but eventually the arch will develop increased flaccidity with widening of the posterior membranous wall.

We recommend the use of these new descriptive terms — MAC types 1, 2, and 3 — and feel the term TBM should be used only when the posterior membranous wall is widened, approaching the 2 to 1 ratio.

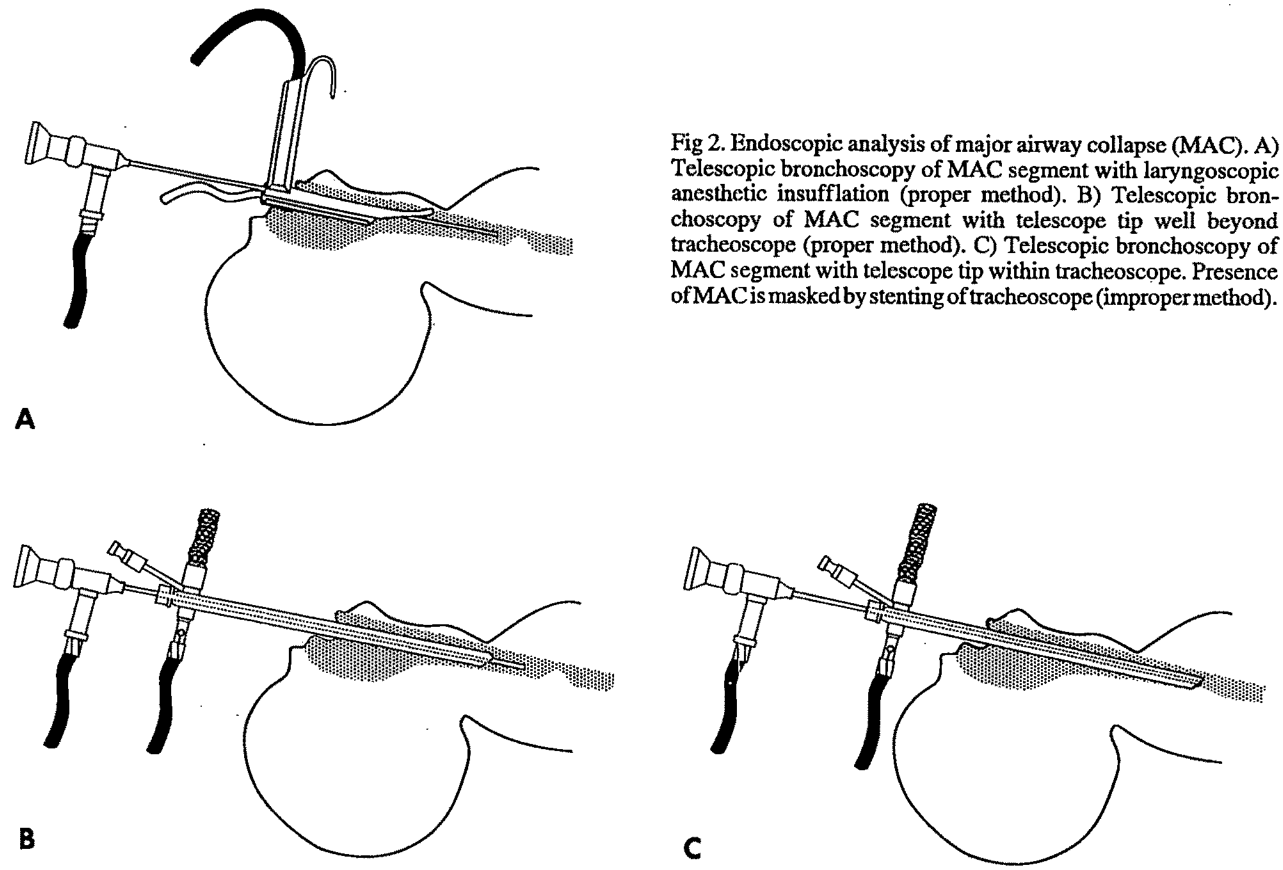


Fig 2. Endoscopic analysis of major airway collapse (MAC). A) Telescopic bronchoscopy of MAC segment with laryngoscopic anesthetic insufflation (proper method). B) Telescopic bronchoscopy of MAC segment with telescope tip well beyond tracheoscope (proper method). C) Telescopic bronchoscopy of MAC segment with telescope tip within tracheoscope. Presence of MAC is masked by stenting of tracheoscope (improper method).

Embryologically, both the trachea and esophagus are formed from the foregut. Major airway collapse type 1 may be caused by a faulty division of the foregut, with the trachea receiving too much tissue during embryonic separation. This theory would account for the widened posterior membranous wall and the strong association of TBM with esophageal atresia and tracheoesophageal fistula. Laryngomalacia is usually not associated with MAC, as the larynx does not develop from the foregut. Maturation of the trachea and bronchus precedes alveolar development,[30] but the conducting airways are still premature at birth; hence, there is a strong association of MAC with prematurity. Tracheobronchomalacia also has been theorized to be secondary to an immature autonomic nervous system.[31] Three (8%) children in our study with TBM had associated neuromuscular anomalies.

In children with respiratory distress suggestive of MAC, a thorough endoscopic examination is critical. Any anesthetic technique using paralysis will mask a flaccid airway. In order to appreciate the presence and degree of malacia, spontaneous ventilation with lightened anesthesia is recommended. A hand-held ventilating laryngoscope[32] is recommended because it allows the surgeon to minimize distortion of the soft laryngotracheal structures; a fixed suspension may lead to misdiagnosis due to iatrogenic contortion of the upper tracheal anatomy. A complete laryngoscopy is performed. Then, instead of passing a rigid ventilating bronchoscope through the glottis, which dilates and masks the malacic segment, a 0° telescope is atraumatically passed into the trachea and main stem bronchi. A 4-mm telescope provides optimal visualization and photodocumentation, but 2.7-mm and 1.9-mm telescopes are now available for small infants or premature neonates, or for babies with stenotic or distorted airways. These telescopes are so small as to not dilate the collapsed airway, and the malacia is readily identified. If a child requires ventilatory support, a ventilating tracheoscope is positioned with its tip just below the glottis. This instrument is simply a bronchoscope without the ventilating side ports on the barrel. The examination is then accomplished with a telescope that extends at least 2 to 4 cm beyond the tracheoscope tip in order to avoid stenting the malacic airway open (Fig 2).

A flexible bronchoscope can be used either in conjunction with spontaneous ventilation with laryngoscopic insufflation or if placed through a tracheoscope. Flexible scopes are now made with controllable distal tips as small as 1.9 mm in diameter; even smaller scopes are available with noncontrollable tips. However, the imagery of flexible fiberoptic scopes is inferior to that of rigid scopes of comparable size.

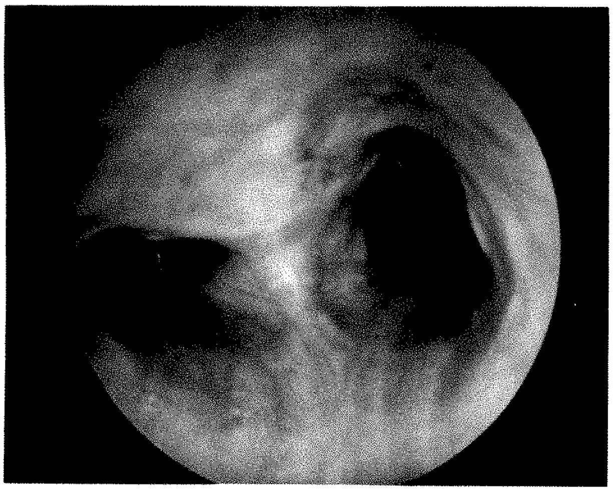


Fig 3. Left main stem bronchomalacia. Ratio of cartilage to posterior membrane approaching 2 to 1 is noted on left. This form of major airway collapse type 2 was due to enlarged and malpositioned pulmonary artery.

Fluoroscopy has been used to study the infant's airway during feeding and crying. Continuous positive airway pressure may be adjusted under fluoroscopic control to evaluate tracheobronchial patency. Unfortunately, radiographic measurements of tracheal and bronchial dimensions have an unacceptably wide range of variation.[33] Overall, fluoroscopy and cine–computed tomography[34] can only suggest the diagnosis of MAC; confirmation must be obtained by endoscopy. Magnetic resonance imaging, computed tomography, angiography, barium swallow studies, and ultrasound may be helpful in determining the cause of MAC (eg, bronchogenic cyst, vascular ring, or congenital heart disease).

It is apparent that a staging system is required to properly define MAC. We suggest that severity be graded by the percentage of airway obstruction noted at end expiration with a system comparable to that used for subglottic stenosis.[35] "Mild" describes less than 70% obstruction, "moderate" is greater than 70% but less than 90%, and "severe" translates to greater than 90% obstruction. It is important to have the anesthetized child breathing spontaneously during endoscopy in order to properly gauge severity.

Couvreur et al[36] reported 127 cases of pediatric TBM. Their criterion for diagnosis is only 50% expiratory airway obstruction noted under local anesthesia without regard to the cartilage-membrane ratio. We are concerned about this technique of examination under local anesthesia in children, as it can result in excessive irritation to the tracheobronchial mucosa leading to spasm and airway compromise. These reactions should not be confused with MAC.

Several authors have reported TBM, like laryngomalacia, to be a self-limiting disease that disappears by the age of 18 to 24 months.[3,36] Although the clinical severity of MAC may decrease over time, the endoscopic findings of the altered cartilage-membrane ratio may persist indefinitely. Wood[37] reported seven children between 7 and 13 years old with intractable cough labeled with a variety of rotating diagnoses and treated by multiple therapeutic regimens. Endoscopy revealed localized tracheomalacia or bronchomalacia in each child. We have performed several endoscopies on older children and adults with MAC previously diagnosed as poorly controlled reactive airway disease or psychogenic coughing.

Because 58% of our children with MAC had associated cardiovascular abnormalities, a thorough cardiac workup to include an electrocardiogram and an echocardiogram is recommended once the diagnosis has been substantiated. The mechanisms relating cardiovascular disorders to lower airway disease (cardiac asthma) may be the link between cardiovascular disorders and MAC.[30]

Bronchomalacia is diagnosed by an altered cartilage-membrane ratio in either or both main stem bronchi and may be associated with congenital lobar emphysema.[15] Left main stem disease seems to be much more common than right-sided bronchomalacia[31] (Fig 3). The left main stem is normally smaller and usually comes off the trachea with greater angulation than the right main stem; this configuration may suggest an abnormal airway when in fact no anomaly exists. Left bronchomalacia may result from left atrial enlargement and increased pulmonary artery pressure.[24] Careful straight and angled telescop-

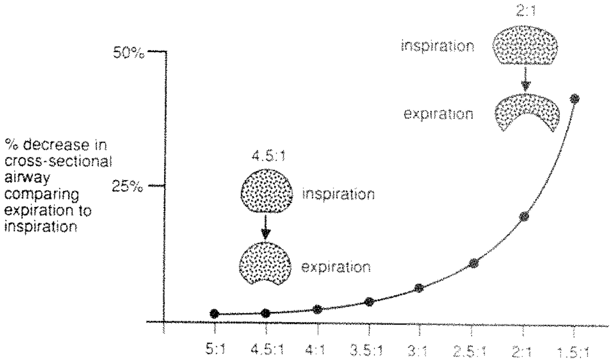


Fig 4. By decreasing ratio of cartilage to posterior membrane from normal value of 4.5 to 1 to value seen with tracheobronchomalacia (2 to 1), dynamic cross-sectional airway area is altered. Normal airway loses only 3.7% of its area on expiration, while malacic airway loses at least 23% of its area when elongated posterior membranous wall collapses on expiration. Cross-sectional airway area comparisons were computed on Zeiss Zidas plotter and do not account for hypotonic cartilage and possible mucosal inflammation further obstructing airway with major airway collapse.

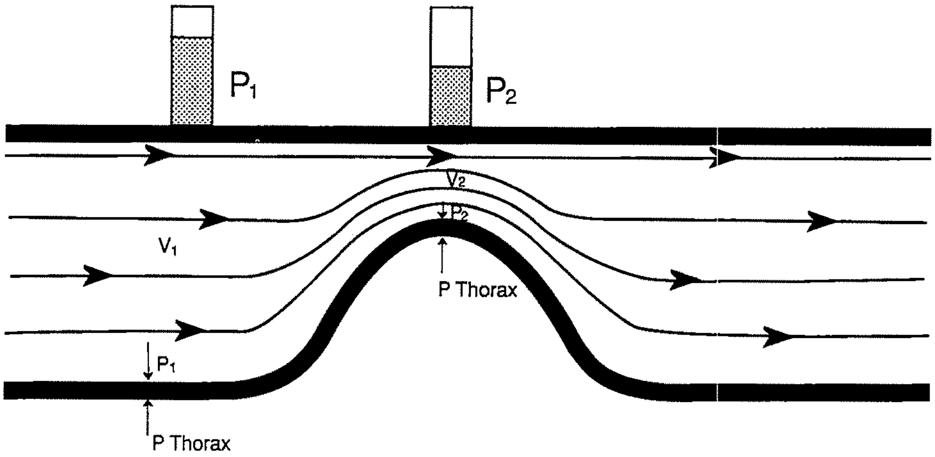


Fig 5. Venturi effect. During expiration, velocity of air in major airway collapse airway (V2) must be greater than laminar airflow in normal airway segment (V1). In accordance with Bernoulli's equation of energy conservation, intratracheal or intrabronchial pressure within MAC airway (P2) must be less than pressure within normal airway segment (P1). Pressure differential causes elevation of flaccid mucosa. This elevation is further enhanced by normal compression of airway secondary to increased intrathoracic pressure of expiration (P Thorax).

ic bronchoscopy is necessary to make an accurate diagnosis.

By using a computer model, the amount of airway obstruction caused by altering the cartilage-membrane ratio and observing the Venturi effect can be graphically measured (Fig 4). Anterior motion of the normal posterior membranous wall during expiration causes only a 3.7% decrease in airway area. Elevation of a malacic posterior membranous wall in a 2 to 1 cartilage-membrane ratio model results in a 23.4% obstruction. Both the anteriorly flattened cartilaginous arch and mucosal irritation with edema from turbulent airflow may worsen the airway obstruction and contribute to the severe expiratory obstruction witnessed during endoscopy. These two dynamic factors are not accounted for in the computer models.

As expected, children with mild MAC tended to fare better than those with the severe form. Endoscopic assessment of severity did not always correlate with the clinical presentation. Some children with endoscopically severe MAC required minimal therapy, while others, with endoscopically mild to moderate MAC, required aggressive intervention.

In our series, treatment of MAC was based on the clinical manifestations of the disease. Clinically mild cases required only observation with respiratory physiotherapy and humidification as necessary. Parents were given reassurance, and the symptoms generally subsided with time. Clinically severe cases require more aggressive management. Prolonged continuous positive airway pressure (5 to 20 cm H2O) may be necessary to minimize clinical symptoms.[38] When possible, treatment is directed at the underlying cause of MAC (eg, vascular anomalies, tracheoesophageal fistula, pectus excavatum, neoplasms). Surgical intervention is warranted when reflex apnea is present or when medical therapy is ineffective.

Although tracheotomy with an elongated tube has been advocated to bypass a malacic segment,[39] we are concerned about this form of therapy for several reasons. Tracheotomy negates the glottic mechanism of increased intratracheal pressure and may weaken the cervical tracheal arches, making decannulation more difficult. The elongated tube may cause obstructive granulation tissue at the distal port, leading to a functional tracheal stenosis. Continuous positive airway pressure is difficult to effectively administer with a new tracheotomy. The risk of infection is increased with a tracheotomy, especially if an intrathoracic procedure such as an aortopexy is being considered. The elongated tube must remain above the carina; otherwise, induced bronchospasm will result. Aortopexy[40] for suspension of the anterior tracheal wall, resection of the malacic segment with reanastomosis,[10] external splinting,[41] and endoscopic placement of expandable stents in the malacic segment[42] are surgical options for severe refractory cases. Mortality has been reported as high as 80%,[11] but depends on the severity of the disease.

Previous reports of TBM state that the onset of symptoms does not begin until at least 1 month after birth and usually much later.[30,43] Our data demonstrate that respiratory obstructive symptoms in the congenital types are almost always noted at birth (95%), but may escalate in severity during the ensuing months. Newborns with cyanosis, apneic attacks, or air trapping with poor ventilation should be promptly evaluated for MAC with endoscopy. Improved outcomes may be enhanced by early diagnosis and aggressive management.

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AIRWAY AND OTHER COMPLICATIONS OF PERCUTANEOUS ENDOSCOPIC GASTROSTOMY IN HEAD AND NECK CANCER PATIENTS

DAVID A. RILEY, MD MELVIN STRAUSS, MD

CLEVELAND, OHIO

The purpose of this study was to look at complications associated with percutaneous endoscopic gastrostomy (PEG) in a group of head and neck cancer patients. We retrospectively reviewed charts of 46 patients referred for PEG. Three of 29 patients without secured airways (10.3%) had acute airway obstruction after administration of sedation for the PEG procedure. Two required emergency tracheostomy. Three additional patients of these 29 (10.3%) presented within 2 months of their PEG attempts with tumor-related airway obstruction requiring emergency tracheostomy. There were no other serious complications noted in our review. We concluded that our group of head and neck cancer patients were at high risk for airway obstruction, especially when sedated, and that the acute risk was not directly associated with the PEG procedure. We also concluded that referral for PEG should be made in anticipation of future nutritional needs and that PEG should not be used only as a late-stage procedure.

KEY WORDS — airway obstruction, complications, head and neck cancer, nutrition, percutaneous endoscopic gastrostomy.

INTRODUCTION

Since percutaneous endoscopic gastrostomy (PEG) was first developed at our institution a decade ago by Gauderer et al,[1] it has become a well-accepted procedure. Head and neck cancer patients are ideal candidates for this procedure, because they generally have functioning upper gastrointestinal tracts. The general consensus has been that the procedure is relatively very safe, with very low rates of morbidity and mortality.[1-7] However, we have observed what seemed to be a large number of major airway complications in a group of head and neck cancer patients undergoing PEG placement. The purpose of this study is to review the complications and other characteristics of a group of head and neck cancer patients who were candidates for PEG at our institution.

MATERIALS AND METHODS

The records of 46 head and neck cancer patients at the University Hospitals of Cleveland (19 patients) and the Cleveland Veterans Administration Hospital (27 patients) who were referred for PEG between February 1, 1984, and February 1, 1990, were retrospectively reviewed. Each record was evaluated for sex and age of the patient, location of tumor, treatment given before or at the time of PEG placement, tumor status at the time of PEG placement, success in placing the PEG, complications of the procedure, length of time of PEG use, and indications for removal of the PEG.

RESULTS

The charts of 46 patients referred for PEG placement were reviewed. There were 39 men and 7 women. The average age was 61, with a range from 46 to 87. Fifteen patients had primary lesions of the hypopharynx, 14 patients had lesions of the oral cavity, 8 patients had oropharyngeal lesions, 4 patients had laryngeal lesions, 1 patient had a primary maxillary sinus lesion, and 1 patient had a tumor of the cervical esophagus; the location of the primary lesion was unknown in 3 patients.

Thirty patients underwent major surgical procedures prior to referral for PEG placement. All but 2 patients received preoperative or postoperative radiotherapy. Most patients had late stage disease (22 patients) at the time of PEG referral or had demonstrated inadequate swallowing after surgery or after beginning radiotherapy (14 patients). Only 4 patients had PEG placement in anticipation of swallowing difficulty (Fig 1).

Of the 46 referrals, PEG was attempted on 39 patients. Thirty-three patients had successful PEG placement after a total of 43 attempts for a 77% success rate. Thirteen patients (28% of the 46) had open gastrostomy (Fig 2). In 7 patients, PEG was not attempted because of anticipated difficulty in passing the endoscope. All but 2 procedures were done in the operating room suite. All but 4 procedures were performed under local anesthesia with intravenous seda-

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From the Department of Otolaryngology–Head and Neck Surgery, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, Ohio.

Presented at the meeting of the American Broncho-Esophagological Association, Waikoloa, Hawaii, May 5-6, 1991.

REPRINTS — Melvin Strauss, MD, Dept of Otolaryngology–Head and Neck Surgery, University Hospitals of Cleveland, Case Western Reserve University, 2074 Abington Rd, Cleveland, OH 44106.

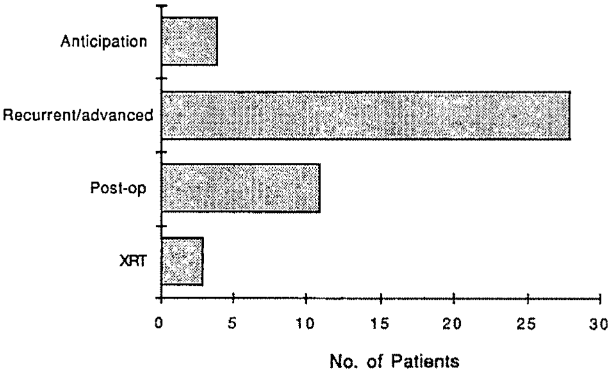

Fig 1. Timing of placement of percutaneous endoscopic gastrostomy. Anticipation — in anticipation of swallowing difficulty, Recurrent/advanced — at time of recurrence of tumor 6 months or more after last surgical procedure, or with advanced inoperable tumor, Post-op — postoperatively after failing to recover adequate swallow, XRT — after or during radiotherapy.

tion.

Several patients had major complications or other difficulties with PEG placement (Fig 3). Three of 29 patients (10.3%) who had not had their airways previously secured by tracheostomy or laryngectomy had acute airway obstruction and respiratory arrest at the time of the PEG procedure. Two of these 3 patients required emergency tracheostomy. Airway difficulties in these patients were encountered after the administration of sedation and prior to the beginning of the actual procedure. One patient experienced a supraventricular tachyarrhythmia at induction of anesthesia. Stricture and tumor obstruction were listed as reasons for inability to pass the endoscope in 5 patients. Two of these 5 patients presented at 17 and 18 days after the unsuccessful attempts with acute airway obstruction requiring emergency tracheostomy. One additional patient who had successful PEG placement presented at 2 months postoperatively with tumor-related airway obstruction requiring emergency tracheostomy.

There were 12 long-term minor complications, most of which consisted of local problems at the gastrostomy tube site on the abdominal wall. There were four leaks. One of these patients required revision of his gastrostomy. There were two occurrences of minor inflammation at the PEG site. Two patients had breakdown at their gastrostomy sites requiring closure of the PEG site and performance of open procedures. One of these patients had tube obstruction and infection at the PEG site. Another patient required psychiatric care after becoming suicidal because of his multiple tubes and associated social changes.

The average length of time of PEG use was 5.5 months. The range was from 2 weeks to 26 months. Only one patient had a PEG removed before dying.

DISCUSSION

In a review of the literature we found five papers addressing the topic of PEG and the head and neck cancer patient.[2-6] The reported success rates were generally high (>90%). Stellato and Gauderer[6] had a lower success rate in patients with head and neck tumors (87%). This compares with a 77% success rate in our study. The fact that the patients in our study had lesions of more advanced stages may explain this finding. Hunter et al[2] reported two episodes of transient respiratory arrest (4%) during the procedure thought to be related to heavy sedation, and another patient who had a near–respiratory arrest that was averted by quickly removing the endoscope. These airway complications led the authors to develop a policy of resecting tumor or performing a tracheostomy in all patients with cancers narrowing the airway before placing a PEG.

Stellato and Gauderer[6] reviewed their experience with PEG in a group of 15 patients with head and neck tumors (11 oropharyngeal and 4 laryngeal). Three patients with advanced oropharyngeal tumors developed severe respiratory compromise. One patient apparently developed respiratory distress during the procedure, and the other 2 prior to the start of the

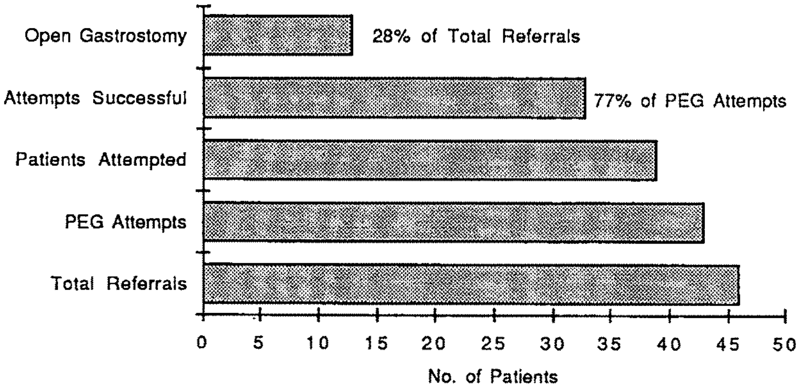

Fig 2. Success of placement of percutaneous endoscopic gastrostomy (PEG). Forty-six patients were referred for gastrostomy (Total Referrals). PEG was attempted (PEG Attempts) 43 times on 39 patients (Patients Attempted). Thirty-three attempts were successful. Open gastrostomy was done on 13 patients because of either failed PEG attempt or anticipation of failure.

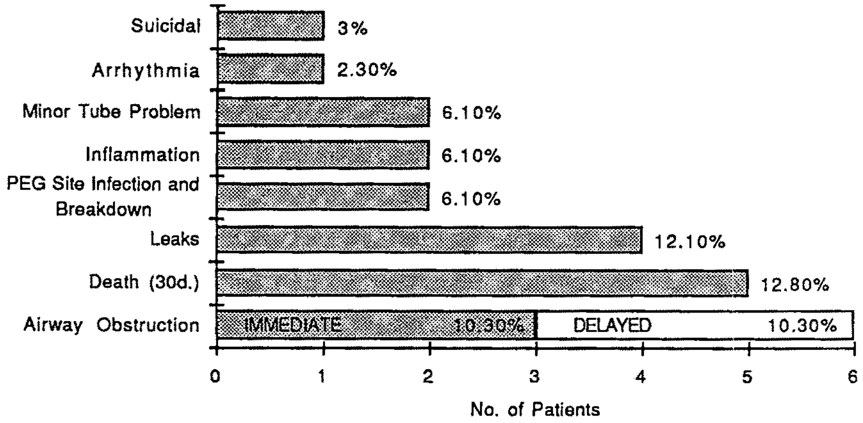

Fig 3. Complications of percutaneous endoscopic gastrostomy (PEG). Denominators are different for various categories and are based on groups identified in Fig 2. Suicidal — suicidal ideation, Arrhythmia — easily controlled supraventricular tachycardia, Minor Tube Problem — tube plugging and dislodgment, Inflammation — redness, tenderness, or excessive granulation tissue at PEG site, Death (30d.) — deaths not directly related to PEG placement within 30 days of placement.

procedure. One ceased breathing after being sedated. (The study of Stellato and Gauderer[6] was done at one of the same institutions as the study now being presented during a different but overlapping time period. No patients with airway obstruction were included in both studies. Thus, combining the findings of both studies, we find six episodes of acute airway distress during PEG procedures at one of our institutions over an approximately 10-year period.) The other authors[3-5] concluded that PEG was safe in head and neck cancer patients.

Only one of the patients in our series had a PEG removed once it was placed. The tendency at our institution seems to be to withhold gastrostomy until the patient's condition is terminal or the patient has declared himself or herself incapable of swallowing effectively over a relatively long period of time. Shike et al[5] and Luetzow et al[4] were able to remove the gastrostomy tube in a high percentage of selected groups of patients (58% and 24%, respectively). Their findings suggest that gastrostomy can be used more aggressively in patients in nonterminal condition by being placed earlier and removed successfully if adequate swallowing function returns. Gardine et al[7] addressed the question of predicting the need for prolonged use of enteral supplementation in the patient with head and neck cancer. In a review of 109 consecutive charts they were able to identify four statistically significant factors predictive of the need for long-term tube feedings. Fifty-eight percent of patients with two or more of the following risk factors required tube feedings for longer than 30 days: 1) stage IV cancers, 2) primary pharyngeal tumors, 3) combined treatment using surgery and irradiation, and 4) preoperative weight loss of more than 4.5 kg (10 lb). They support the early placement of gastrostomy tubes in these patients. Hunter et al[2] also advocated early PEG placement in these patients, preferably before radical surgery or soon afterward.

The results of our study suggest that patients with advanced head and neck cancers with or without a history of major surgery are at risk (10.3%) for life-threatening airway obstruction if they are subjected to instrumentation and/or sedation. Two additional patients who presented with airway obstruction approximately 2½ weeks after attempted PEG may represent true complications of this procedure. The high overall incidence of airway obstruction in this study (20.6% combined acute and delayed) certainly reflects an underlying predisposition for patients with large tumors in their airways to have airway obstruction. Our airway complication rate was calculated after subtracting the 10 patients with previous total laryngectomy and tracheostomy who therefore were not at risk for losing their airways. The patients in our study seemed to have been referred for PEG at a more advanced stage of disease and possibly a more advanced state of malnutrition than those in other reviews. Malnutrition may have contributed to a higher complication rate.[8] A recent study established that patients with normal upper airways having upper and lower endoscopy tend to have arterial oxygen desaturation.[9] Fifteen percent of patients having upper endoscopy desaturated to 85% or less. Possible reasons suggested for the observed desaturations include sedation, large endoscope size, and aspiration of minute amounts of gastric contents. Patients with pharyngeal and oral cancers may be at even greater risk for desaturation and subsequent respiratory distress than patients with normal airways.

CONCLUSION

Patients in our series of head and neck cancer patients undergoing PEG procedures experienced a high rate of serious airway problems during and following PEG placement. This has been reported and addressed as a complication only in the general surgery literature. We strongly suggest the following.

1. The practice of placing a PEG by using extensive intravenous sedation or general anesthesia in

patients with advanced head and neck cancers should be avoided unless the tumor has been surgically removed or the airway has been secured by placement of a tracheostoma. At the very least, all equipment, drugs, and personnel required for securing an airway emergently should be immediately available.

2. Patients with advanced head and neck tumors and without secured airways should have PEG procedures performed in an operating room.

3. Patients at risk for requiring long-term enteral feeding should be identified and referred earlier for PEG placement; PEG should not be used only as a late-stage procedure.

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ACQUIRED LARYNGOMALACIA: EPIGLOTTIS PROLAPSE AS A CAUSE OF AIRWAY OBSTRUCTION

PEAK WOO, MD

SYRACUSE, NEW YORK

Epiglottis prolapse during inspiration is an unusual cause of upper airway obstruction. It occurs primarily in patients who have lost pharyngeal airway support because of previous surgery or after head injury and coma. Eight cases of epiglottis prolapse are presented. One patient had epiglottis prolapse after resection of floor of mouth cancer and another after laryngeal fracture. The rest of the cases were seen in patients recovering from head injury and coma. Videolaryngoscopy shows the larynx to assume an ovoid shape within the pharynx. There is loss of the usual anterior to posterior pharyngeal and laryngeal dimension. The epiglottis is in a more horizontal position at rest. During inspiration, the epiglottis prolapses into the endolarynx, causing subtotal airway obstruction. Laryngeal obstruction due to epiglottis prolapse can prevent decannulation in the head-injured and can be the cause of obstructive sleep apnea. Endoscopic carbon dioxide laser epiglottectomy was successful in management of these cases.

KEY WORDS —acquired laryngomalacia, airway obstruction, epiglottis prolapse.

INTRODUCTION

Supraglottic airway collapse is a well-recognized cause of laryngeal stridor in children. Laryngomalacia is the most common cause of stridor in newborns.[1] However, collapse of normal supraglottic structures in adults has rarely been described as a cause of airway obstruction. Templer et al[2] described a case of congenital laryngeal anomaly persisting into adulthood. Peron et al[3] reported on their experience with treatment of redundant aryepiglottic folds as a cause of stridor. Their series of seven older patients had flaccid and redundant aryepiglottic folds as a cause of stridor occurring after central nervous system (CNS) injury. This was attributed to CNS disease in their patients. Kletzker and Bastian[4] also reported three cases of acquired airway obstruction due to histologically normal supraglottic soft tissue. These patients also had redundant aryepiglottic folds as the cause of airway obstruction. They were treated successfully by endoscopic removal of the redundant aryepiglottic folds. Our report presents eight additional cases of acquired supraglottic airway collapse as a cause of stridor. Unlike the other reports, the cause of airway obstruction in this series was prolapse of the epiglottis during inspiration. This airflow induced collapse of the epiglottis, which may also be termed acquired laryngomalacia, was the cause of severe upper airway obstruction in adults.

MATERIALS AND METHODS

Eight cases of epiglottis prolapse causing severe airway obstruction have been identified. Six patients were evaluated because they could not be decannulated after tracheostomy. All had severe CNS insults; all had severe stridor and airway obstruction upon being capped during the decannulation process. All six were in the process of recovering from coma. Two other patients were evaluated for progressive obstructive sleep apnea after previous surgery involving the larynx and pharynx.

CASE REPORTS

Case 1. A 19-year-old, previously healthy man was involved in a motor vehicle accident on July 3, 1988. He sustained extensive closed head injury requiring ventriculostomy, posterior fossa craniotomy for evacuation of hematoma, and a ventriculoperitoneal shunt. An uncomplicated tracheostomy was performed 10 days after admission. On September 14, the otolaryngology service was consulted to evaluate severe stridor occurring when his tracheostomy tube was capped. His neurologic condition was, at this time, improved enough to consider decannulation. He was aware, awake, and able to cough on command. Flexible laryngoscopy and tracheobronchoscopy was done. It showed a sizeable amount of peristomal granulation tissue and a flaccid, horizontally positioned epiglottis (Fig 1A). The peristomal granulation tissue was believed to be the source of stridor. On October 18, he underwent complete excision of suprastomal granulation tissue by use of the carbon dioxide (CO_2) laser bronchoscope. He was decannulated the next day. Immediately after decannulation, severe inspiratory stridor with oxygen desaturation occurred. The patient was reexamined. On fiberoptic laryngoscopy, the epiglottis was seen to be sucked into the larynx

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From the Department of Otolaryngology, State University of New York Health Science Center at Syracuse, Syracuse, New York.

Presented at the meeting of the American Laryngological Association, Waikoloa, Hawaii, May 4-5, 1991.

REPRINTS — Peak Woo, MD, Dept of Otolaryngology, SUNY Health Science Center at Syracuse, 750 E Adams St, Syracuse, NY 13210.

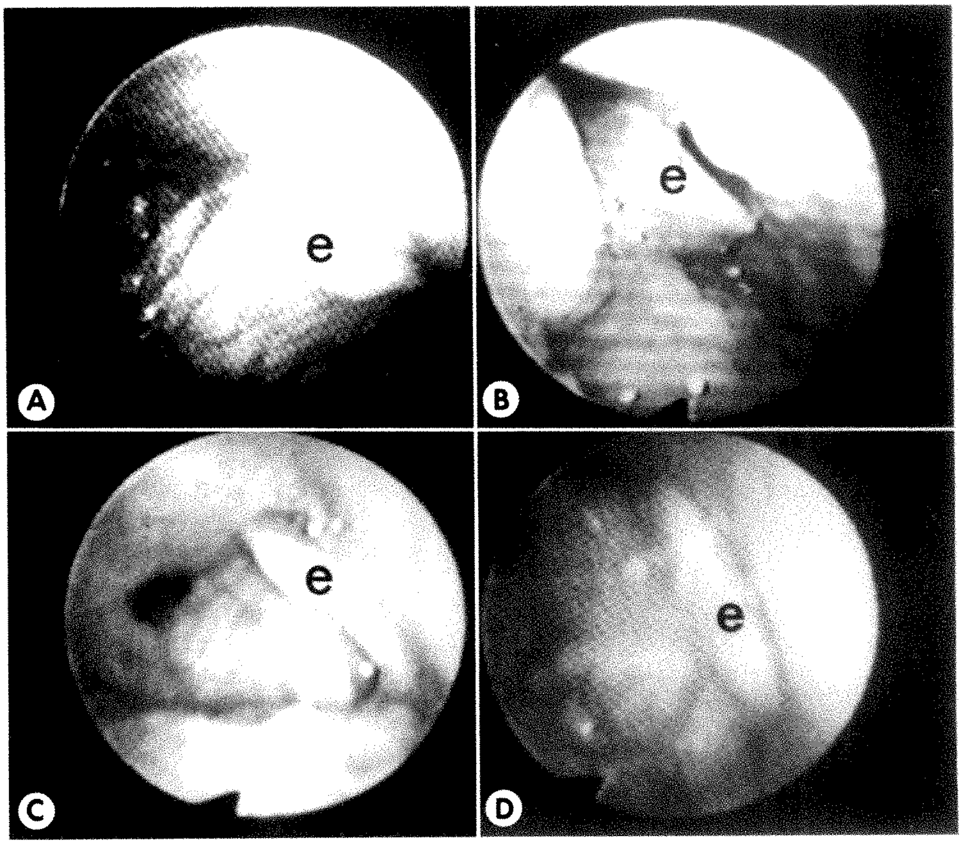

Fig 1. Photographs of epiglottis prolapse during inspiration in four patients. e — tip of epiglottis. A) (Case 1) Notice posterior and horizontal tilt of epiglottis. B) (Case 3) Notice impaction of epiglottis against posterior pharyngeal wall. C) (Case 4) Notice subtotal airway occlusion. D) Case 5.

during inspiration, thus causing subtotal upper airway obstruction. Examination of the rest of the larynx and trachea revealed normal findings. He was returned to the operating room. A partial epiglottis resection with the CO2 laser was performed through the operating laryngoscope. Surgical excision consisted of resection of the superior half of the suprahyoid epiglottis. After this endoscopic procedure, there was complete relief of inspiratory stridor and the patient was discharged home decannulated and without stridor. Follow-up examination at 2 years showed excellent swallow function and respiration without airway obstruction. Laryngoscopy showed a shortened epiglottis in an upright posture without prolapse.

Case 2. A 68-year-old woman presented with a T4N0M0 squamous cell carcinoma of the oral vestibule due to smokeless tobacco. She was treated in February 1986 by a composite resection. Resection margins included all suprahyoid structures, the mandible, and the entire floor of the mouth. She was reconstructed with a large myocutaneous flap and a mandible reconstruction plate (AO-ASIF). She did well until June 8, 1988, when she was reevaluated for

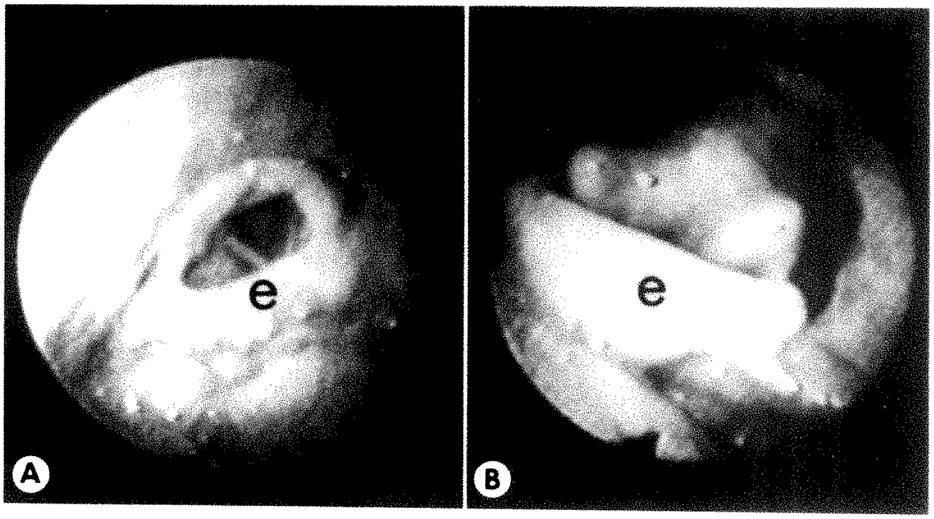

Fig 2. (Case 2) Photographs of larynx during inspiration. e — epiglottis. A) Partial epiglottectomy relieves flow-induced epiglottis prolapse without major resection of normal structures. B) Preoperative view. Larynx is obscured by epiglottis with symptoms of nocturnal airway obstruction.

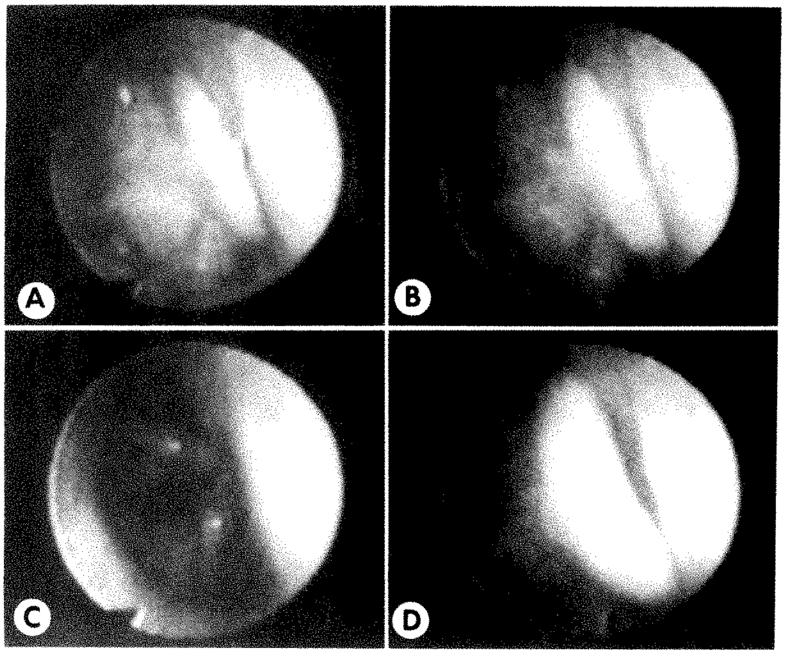

Fig 3. (Case 4) Severe obstruction during inspiration. Sequential frames of epiglottis and larynx during respiration. A) Epiglottis prolapse during inspiration. B) End of inspiration. C) Expiration. D) Beginning of inspiration.

complaints of daytime somnolence, nocturnal apnea, and stridor. When placed in a supine position, she became quite dyspneic. Flexible laryngoscopic examination and radiographic tests failed to show a recurrence. However, on fiberoptic laryngoscopy, the epiglottis was tilted in a posterior and horizontal position. With each inspiration, the epiglottis fluttered inferiorly and obstructed the laryngeal inlet. The patient was treated by tracheostomy followed by CO2 laser endoscopic epiglottectomy to remove the superior half of the suprahyoid epiglottis.

She tolerated the procedure well and was decannulated immediately after the operation without incident. Immediately, she was able to sleep better and was able to lie flat. Follow-up at 2 years has shown an excellent airway with complete relief of obstructive sleep apnea. Figure 2 shows the preoperative view and the postoperative result. A better airway is observed after surgery.

Case 3. A 32-year-old man had blunt trauma to the neck with laryngeal fracture in 1984. He was treated

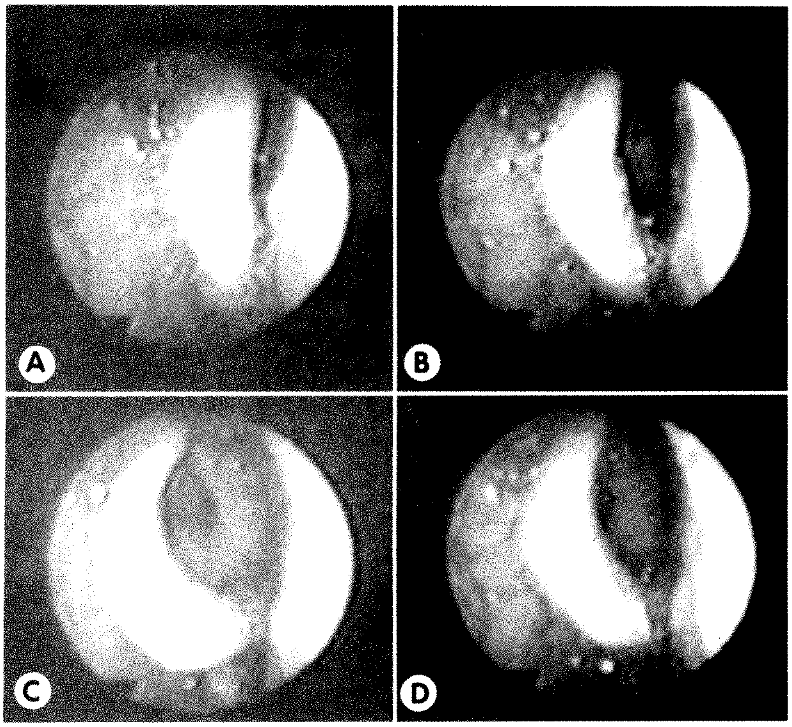

Fig 4. (Case 4) Mild obstruction. Sequential frames during respiration. Same patient as in Fig 3, 6 months later. A) Epiglottis prolapse during inspiration. B) End of inspiration. C) Expiration. D) Beginning of inspiration.

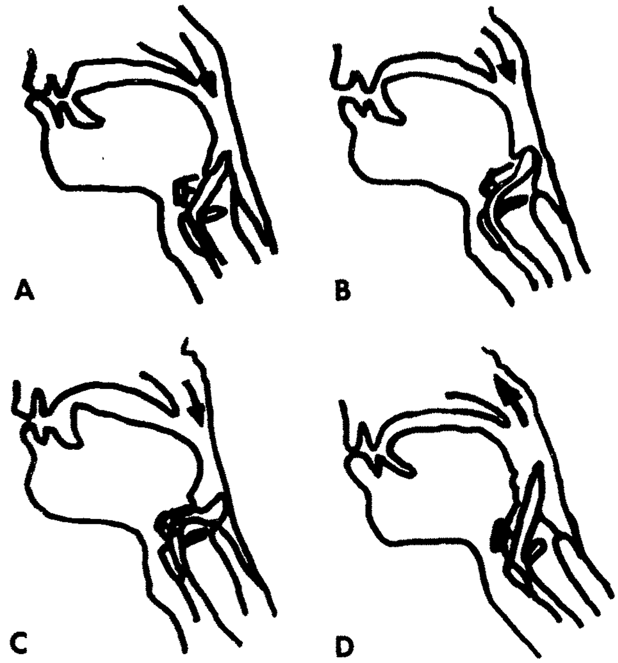

Fig 5. Schematic of flow-related collapse of epiglottis. A) Beginning of inspiration. B) Midcycle inspiration. C) Complete collapse at end of inspiration. D) Relief of airway obstruction during expiration.

elsewhere with thyrotomy, laryngeal stenting, and tracheostomy. He was decannulated successfully in 1985 after several operations. In June 1988, he came to the otolaryngology clinic because of progressive dyspnea with exertion, nocturnal airway obstruction, and inability to lie flat without dyspnea. Flexible fiberoptic laryngoscopy showed the following: the lingual tonsils were large, the hypopharynx was crowded, and the posterior tip of the epiglottis was touching the posterior pharyngeal wall (Fig 1B). With each inspiration, the epiglottis was drawn posteriorly into a horizontal position and collapsed against the posterior hypopharyngeal wall, thereby obstructing the airway. The vocal folds were mobile and the trachea was open. In addition to these findings, the aryepiglottic folds and the arytenoids also appeared swollen and redundant. The patient was treated by partial CO2 laser epiglottectomy, and resection of redundant aryepiglottic folds. He had immediate relief of his airway symptoms. He remained free of symptoms 6 months later.

Case 4. A 49-year-old man was struck by a motor vehicle on May 23, 1988. He sustained closed head injury with coma. A tracheostomy was performed shortly after his injury. He was transferred to a neurologic rehabilitation center. On July 6, fiberoptic laryngoscopy was done to assess laryngeal function prior to attempted decannulation.

Fiberoptic examination showed a narrowed hypopharynx in that the tongue base was close to the posterior pharyngeal wall. The epiglottis was tilted in a horizontal position, occluding the larynx with each inspiratory effort. The patient was also aspirating his oral and pharyngeal secretions. Because of his aspiration, decannulation was delayed. Reexamination 6 months later showed a man with dramatically improved mental status, less aspiration, and markedly less epiglottis prolapse on inspiration. The hypopharyngeal dimension was also much wider and the epiglottis was less horizontally placed. Although the epiglottis still fluttered with inspiration, it was no longer touching the posterior pharyngeal wall. The patient was decannulated at that time without difficulty.

Reexamination 6 months later showed further improvement in mental status. Laryngoscopy revealed a normal-appearing larynx without posterior epiglottis prolapse or epiglottis flutter.

RESULTS

As part of this study, a retrospective review of videolaryngoscopy from 118 patients with severe closed head injuries was done. Of these, supraglottic airway obstruction due to epiglottis prolapse or epiglottis flutter was identified in 13 cases. The degree of obstruction varied from mild to severe. While only 6 patients were identified as having severe epiglottis prolapse as the cause for failure of decannulation, the rest had milder forms of obstruction by an abnormal epiglottis that contributed to stridor. All these patients were healthy prior to their neurologic insult. The types of central neurologic injury included diffuse anoxic injury, intracerebral hemorrhage, hydrocephalus, brain stem infarction, and closed head injury. All the patients with acquired epiglottis prolapse were in various degrees of coma on initial examination. Most still had a low score on the Glasgow Coma Scale. Common fiberoptic laryngoscopy findings in these patients included poor voluntary laryngeal and tongue control, poor neuromotor control to achieve pharyngeal dilation, and poor neuromotor control of deglutition. In these patients, despite their being examined in an upright posture, the epiglottis is tipped posteriorly and assumes a slightly horizontal posture. The tip of the epiglottis is in close proximity to the posterior pharyngeal wall. With inspiration, the epiglottis flutters and is displaced posteriorly and inferiorly. Upper airway obstruction occurs by impaction of the epiglottis against the posterior pharyngeal wall or by prolapse of the epiglottis onto the arytenoid and aryepiglottic folds.

The severity of airway obstruction is flow rate–dependent and is made worse by vigorous inspiratory efforts. Figure 3 is a sequential photograph of the

CLINICAL CHARACTERISTICS OF EIGHT PATIENTS WITH ACQUIRED LARYNGOMALACIA

Case	Age	Sex	Date of Injury	Date of Exam	Cause	Laryngeal Findings	Other Findings	Treatment	Outcome	Complications
1	19	M	7/3/88	9/14/88	Motor vehicle accident, coma	Epiglottis prolapse with inspiration	Peristomal granulation	Laser epiglottectomy, laser bronchoscopy	Decannulated	None
2	68	F	1/3/86	6/8/88	Suprahyoid cancer resection	Posterior and horizontal position of epiglottis	None	Laser epiglottectomy	Decannulated	None
3	27	M	1/5/86	7/2/88	Laryngeal fracture	Epiglottis prolapse with inspiration	Redundant aryepiglottic fold	Laser epiglottectomy, resection of arytenoid mucosa	Improved	None
4	49	M	5/23/88	2/6/88	Traumatic head injury	Epiglottis prolapse, epiglottis flutter	Aspiration	Observation	Decannulated	None
5	37	F	10/28/89	2/14/90	Bleeding aneurysm	Epiglottis prolapse with inspiration	Tracheal granulation	Laser epiglottectomy	Decannulated	Aspiration at 1 wk
6	26	F	1/29/89	6/28/89	Closed head injury	Epiglottis prolapse, posterior laryngeal web	Tracheal granulation	Epiglottectomy, web lysis	Decannulated	None
7	52	M	10/1/89	1/10/90	Brain stem stroke	Epiglottis prolapse, severe aspiration	Pharyngeal myoclonus	Total laryngectomy for aspiration	Laryngectomy	None
8	21	F	12/5/88	1/4/89	Closed head injury	Epiglottis prolapse, mild aspiration	Large tracheostomy tube	Observation, tube change	Decannulated	None

larynx (case 4) during respiration, showing the severe degree of airway obstruction occurring during inspiration. Figure 4 (case 4) shows the same patient after ventriculoperitoneal shunting followed by improved mental status. The improved mental status correlated well with improvements in the degree of supraglottic airway collapse.

Figure 5 is a schematic representation of the airflow-related collapse of the epiglottis. In the mild cases, only epiglottis fluttering was seen. In patients with severe obstruction, the epiglottis actually prolapsed into the supraglottic larynx and caused total airway obstruction during inspiration.

The Table summarizes the clinical data on the patients and their treatment. In four of the six head injury patients, other laryngotracheal abnormalities were identified. These included a posterior laryngeal web, suprastomal stenosis, and incomplete laryngeal abduction. However, in each case, the major cause of stridor was epiglottis prolapse (see Table). Corrective surgery by partial epiglottectomy relieved the symptoms in three of the six patients. In those not treated by surgery, improved mental status resulted in better neuromotor control, better pharyngeal dilation, and less epiglottis prolapse. This improvement in pharyngeal and laryngeal function correlated clinically with a decrease in degree of stridor. The cause of acquired upper airway collapse after head injury is believed to be loss of pharyngeal motor control. Although histologically normal, normal respiratory function is nevertheless compromised by epiglottis prolapse due to loss of central neuromotor control.

The other two patients had delayed onset of upper airway obstruction after head and neck surgery. One had surgical resection of the suprahyoid musculature for cancer, and the other had laryngeal fracture, thyrotomy, and injury to the hyoepiglottic ligament.

Both patients showed epiglottis prolapse that occurred several years after head and neck surgery. The acquired condition of epiglottis prolapse is probably related to initial loss of airway support from surgery, followed by flow-related pull on the epiglottis, resulting in further epiglottis prolapse and airway obstruction.

DISCUSSION

These cases of acquired laryngomalacia may have mechanisms of supraglottic airway collapse similar to those described in infants.[5] Mechanisms of laryngeal obstruction in children with laryngomalacia may include 1) inspiratory collapse of the arytenoid cartilages, 2) collapse of the tubular epiglottis, and 3) epiglottis displacement posteriorly to create a seal against the posterior pharyngeal wall. While the most common cause of laryngomalacia in children is anterior collapse of the aryepiglottic folds and the cuneiform cartilage, this was not seen in adult cases. The cases presented in this paper have posterior folding or "prolapse" of the epiglottis as the cause of airway obstruction.

Central nervous system disorders as a comorbidity in laryngomalacia has been recognized by previous authors. Belmont and Grundfast[6] noted a high association of neurologic disorders such as hypotonia and central apnea with congenital laryngeal stridor. Apley,[7] in his follow-up survey of 80 cases of infants with stridor, also noted a high incidence of disorders of the CNS, as compared with normal infants. He noted the abnormality as primarily one of movement, whereby the epiglottis and arytenoids are drawn into the larynx on inspiration. Laryngeal findings in our study are similar to the description noted in their paper. They include pharyngeal hypotonia, inspiratory movement of the epiglottis, and airway obstruction. The difference here is the acquired nature of laryngeal findings. All the patients presented here were previously healthy; they sustained a CNS insult or other injuries, developed epiglottis prolapse, and in some cases spontaneously resolved this condition with improvements in neural function.

These patients with acquired airway collapse hint at the importance of both extralaryngeal neuromotor control and intrinsic laryngeal structure to maintain airway support and patency. Kelemen, in his study on congenital laryngeal stridor, stated, "The suspension of the epiglottis is extremely loose. This fact is demonstrated (1) histologically by the areolar-adipose preepiglottic cushion, which continues...until it reaches the top of the ventricular appendix..."[8(p268)] Events leading to acquired laryngomalacia in our patients may follow these hypothetical steps: 1) loss of neuromotor control of the pharynx by CNS injury or loss of anatomic and muscular support by surgical resection of suprahyoid musculature and/or injury to the hyoepiglottic ligament; 2) loss of neuromotor control that narrows the anterior to posterior pharyngeal dimension, tipping the epiglottis horizontally against the posterior pharyngeal wall; 3) with inspiration, fast flow across a constricted pharyngeal orifice and the laryngeal surface of the epiglottis, resulting in a high negative pressure gradient (because of the Bernoulli phenomenon, this gradient results in sucking of the epiglottis into the larynx and causes inspiratory fluttering of the epiglottis); and 4) prolonged pull on the epiglottis, resulting in further weakening of the epiglottis suspensory ligaments and worsening airway obstruction.

Recognition of epiglottis prolapse as a cause of airway obstruction may prevent unnecessary long-term tracheostomy dependency and repeated surgery. In case 1, the failure to recognize this entity resulted in a second surgical procedure.

Treatment for this condition is directed toward reversal of the flow constriction. In those with spontaneous resolution of head injury, improved pharyngeal control and improved pharyngeal tone results in a widened anterior to posterior pharyngeal diameter and spontaneous improvement in respiratory difficulties. In those with no spontaneous improvement, the principle of surgical treatment is similar to those of treatments proposed for congenital laryngomalacia.[9,10] Carbon dioxide laser epiglottectomy or laser epiglottoplasty is performed to reverse the flow-induced obstruction. By trimming the top half of the suprahyoid epiglottis, flow-induced epiglottis prolapse is alleviated. Partial epiglottectomy has been tolerated well with little effect on swallow function. Although one patient had worsened aspiration for 1 to 2 weeks after laser epiglottectomy, no lasting sequelae have been observed after epiglottectomy.

In summary, acquired epiglottis prolapse may be a cause of obstructive apnea and failure to be decannulated after tracheostomy. Eight cases are reported. Most patients have central neurologic injury resulting in poor pharyngeal control and support; some patients may develop this condition after surgical resection of suprahyoid muscles and injury of epiglottis support. Clinical history and symptoms include inspiratory stridor, obstructive sleep apnea, and positional dyspnea. Fiberoptic laryngoscopy and video documentation is most useful in establishing the diagnosis. Awareness of this entity helps in planning appropriate surgical and nonsurgical treatment.

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PHYSIOLOGIC ASSESSMENT OF ARYTENOID ADDUCTION

DAVID H. SLAVIT, MD
BROOKLYN, NEW YORK

NICOLAS E. MARAGOS, MD
ROCHESTER, MINNESOTA

Arytenoid adduction as described by Isshiki is a surgical technique used to improve vocal quality by adducting the arytenoid cartilage of a paralyzed vocal fold, medializing the fold, and closing the posterior glottic aperture. Surgical results of this operation were evaluated by preoperative and postoperative voice recordings, laryngoscopy, and stroboscopy. Objective measurements of vocal jitter, shimmer, and signal to noise ratio were done to assess changes in the vibratory patterns, and analysis of data from 12 patients revealed improved glottic function postoperatively. Often an anterior medialization procedure, primarily a type I thyroplasty, was used to supplement the posterior medialization achieved by adduction of the arytenoid. Arytenoid adduction is recommended as an effective and reliable treatment for posterior glottic insufficiency.

KEY WORDS — arytenoid adduction, larynx, vocal fold paralysis, voice.

INTRODUCTION

Arytenoid adduction as described by Isshiki et al[1,2] is a surgical technique used to improve vocal quality and glottic competence. It has been used primarily in Japan since the 1970s, but recently has been used by various otolaryngologists in the United States. This procedure adducts and rotates the arytenoid cartilage of the paralyzed vocal fold, medializing the fold and closing the posterior glottic aperture. It is especially indicated for cases with a wide glottic chink. Because there is no direct surgical intervention through the vocal fold mucosa, postoperative scarring of the fold that would hinder vibration is avoided.

The use of Teflon injection or a type I thyroplasty[2,3] to medialize the vocal fold is usually unsuccessful in correcting a large posterior glottic defect. The reasons for this are various, but among the most important are 1) cricoarytenoid joint ankylosis in up to one third of patients with long-standing vocal fold paralysis, 2) inability to inject Teflon lateral to the arytenoid cartilage except toward the vocal process, and 3) inability to access the area lateral to the arytenoid in a type I thyroplasty unless the inner perichondrium of the thyroid cartilage is violated. On the other hand, the arytenoid adduction procedure allows for direct surgical correction of a posterior glottic deficiency. This procedure also pulls the arytenoid cartilage inferiorly, lowering the level of the paralyzed fold, and correcting the difference of levels of the vocal fold often seen with a large posterior glottic chink. The paralyzed fold is in a higher position than the nonparalyzed fold because of the characteristics of the cricoarytenoid joint.[4,5] Posterior glottic deficiencies are often seen with a combined paralysis of the ipsilateral superior and recurrent laryngeal nerves. These paralyses may be synchronous (eg, high vagal lesion) or time-delayed, but the underlying result is lateralization of the entire vocal fold through lateralization and lateral rotation of the arytenoid cartilage. In some of these patients an "anterior" medialization procedure (Teflon injection or type I thyroplasty) may need to be performed in conjunction with an arytenoid adduction to compensate for the atrophy and bowing of the anterior membranous vocal fold.

The physiologic assessment of patients undergoing arytenoid adduction procedures is presented. The physiologic parameters assessed included the measurements of vocal jitter and shimmer along with the aperiodicity signal to noise ratio (SNR) of the acoustic signal. Measures of sequential cycle-to-cycle variations of frequency (jitter) and amplitude (shimmer) during sustained vowel phonation have been implicated as physical correlates of rough or hoarse voice.[6-9] The SNR has also been useful in describing characteristics of normal and pathologic voice.[8] Of particular interest is the preoperative evaluation and determination of whether the procedure to correct a posterior glottic deficiency should include an arytenoid adduction with or without a simultaneous anterior medialization procedure.

MATERIALS AND METHODS

Patients. From November 1, 1988, to September 30, 1990, 12 patients underwent arytenoid adduction at the Mayo Clinic. Seven of the 12 patients were severely dysphonic or aphonic. Six cases were associated with a high vagal lesion. Surgery within the thorax was the cause of the vocal fold paralysis in 3 cases, and endotracheal intubation was associated with another case. A viral cause was suspected in the other 2 patients. All patients had lateralization of the vocal fold with a significant posterior glottic defect.

Instrumentation for Physiologic Assessment of

From the Department of Otolaryngology, Long Island College Hospital-State University of New York Health Science Center, Brooklyn, New York (Slavit), and the Department of Otorhinolaryngology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota (Maragos).

Presented at the meeting of the American Laryngological Association, Waikoloa, Hawaii, May 4-5, 1991.

REPRINTS — Nicolas E. Maragos, MD, Dept of Otorhinolaryngology, Mayo Clinic, 200 First St SW, Rochester, MN 55905.

TABLE 1. COMPUTATIONAL FORMULAS FOR JITTER AND SHIMMER IN VOICE ANALYSIS

$$\% \text{ Jitter} = \frac{\sum_{i=1}^{N-1} | Pi - Pi + 1 | / N - 1}{\sum_{l=1}^{N} (Pi) / N} = \frac{\text{Average cycle-to-cycle difference in period}}{\text{Average period}}$$

$$\% \text{ Shimmer} = \frac{\sum_{i=1}^{N-1} | Ai - Ai + 1 | / N - 1}{\sum_{i=1}^{N} (Pi) / N} = \frac{\text{Average cycle-to-cycle difference in amplitude}}{\text{Average amplitude}}$$

Pi — period of i^{th} cycle, Ai — amplitude of i^{th} cycle, N — number of cycles.

TABLE 2. VIDEO LARYNGOSCOPY

- Respiration
  - Regular
  - Rapid, forceful
- Valsalva maneuver followed by slow release
- Vowel prolongation "Aaaaaa" and "Eeeeee"
- Continuous scale
- Repeat "he" rapidly
- Repeat "key" rapidly
- Repeat "Cree" rapidly
- Coup de glot (grunt)
- Have patient read the following:

"You wish to know all about my grandfather. Well, he is nearly 93 years old, yet he still thinks as swiftly as ever. He dresses himself in an old black frock coat, usually several buttons missing. A long beard clings to his chin, giving those who observe him a pronounced feeling of the utmost respect."

Voice. Eleven patients completed preoperative and postoperative evaluation that included a combination of high-quality voice recording, video laryngoscopy, and laryngeal stroboscopy.[10] One patient died of unrelated causes prior to the completion of the postoperative voice analysis.

Voice recordings were obtained with an AKG D330T microphone and an Onkyo TA-W88 tape machine. An AST 20858 microcomputer with an 80287 math coprocessor and ASYSTANT software (ASYST Technologies) for high-speed data acquisition and analysis was used. Video laryngoscopy and stroboscopy were performed with a Bruel & Kjaer stroboscopic unit. An Olympus ENF P2 or ENF L3 nasopharyngoscope or a Nagashima 70° rigid telescope was used to visualize the larynx.

Speech Task, Data Aquisition, and Data Analysis. To determine jitter, shimmer, and SNR, subjects produced a steady-state vowel /a/ for as long as possible at a comfortable volume and pitch. During vowel prolongation the acoustic signal was recorded. The acoustic signal was then low-pass-filtered at 500 Hz and sampled at 20 kHz before being stored on the hard disk.

The computer software program was used to determine the vocal jitter, vocal shimmer, and SNR. Also determined was the fundamental frequency. One second of the waveform from the middle portion of each vowel prolongation was used to calculate these parameters. The computational formulas used for jitter and shimmer are shown in Table 1. Jitter was calculated as the ratio of the sum of the absolute cycle-to-cycle variability in the period to the mean period and was expressed as a percentage. Shimmer was determined as the ratio of the absolute cycle-to-cycle variability in amplitude to the mean amplitude multiplied by 100 and was expressed as a percentage. The SNR is the ratio of total energy in the speech signal to energy in the aperiodic component of the signal and was expressed in decibels.

Laryngoscopy was performed preoperatively and postoperatively by our standard laryngeal assessment recording techniques (Table 2). Laryngeal stroboscopy, preferably with the 70° rigid telescope to avoid any distortional effects due to displacement of the flexible nasopharyngoscope off midline, was also performed to assess the vibratory characteristics of the vocal folds.

Surgical Technique. A technique similar to that described by Isshiki et al[1,2] was used. These procedures were performed under local anesthesia so that the patients could phonate on request during the surgical procedure.

A horizontal incision was made in the anterior neck at the level of the vocal fold and was extended slightly further laterally on the side of the vocal fold paralysis. Subplatysmal skin flaps were raised superiorly and inferiorly. The strap muscles were then split in the midline and the thyroid cartilage was exposed. The posterior edge of the thyroid ala was exposed on the paralyzed side and the thyropharyngeal muscle was incised. With a small hook, the posterior edge of the thyroid cartilage was retracted and rotated anteriorly. The perichondrium at the posterior edge of the thyroid ala was incised and elevated subperichondrally along the posterior margin and inner surface of the thyroid cartilage. The cricothyroid joint was then dislocated and the thyroid cartilage further rotated anteriorly with exposure of the region of the pyriform sinus. In most cases, a 1.0-cm vertical strip of cartilage from this area was removed for better exposure. This strip included the inferior cornu and posterior edge of the thyroid ala to approximately 8 mm above the posterior projection of the vocal fold level. The superior cornu with muscular attachments remained intact. The mucosa of the pyriform sinus recess was then elevated upward and posteriorly to carefully expose and identify the posterior cricoarytenoid muscle. We identified the muscular process by tracing the fibers of the posterior cricoarytenoid muscle superiorly and anteriorly to their junction with the thyroarytenoid muscle. The muscular process of the arytenoid was also noted to be at the level of the vocal fold, approximately 1 cm above the cricothyroid joint in an oblique direction, and could also be identified by following the posterolateral cricoid cartilage superiorly to the cricoarytenoid joint. Once the muscular process of the arytenoid was identified, the cricoarytenoid joint was opened laterally only. Two 4-0 nylon sutures on Keith needles were passed through the anterior aspect of the thyroid cartilage to the region of the muscular process. Two holes were drilled through the anterior cartilage to facilitate suture placement, the holes being approximately 5 mm and 10 mm from the midline and 3 mm inferior to the lower border of a possible type I thyroplasty window. These two sutures were passed through the thyroid cartilage along its caudal and inferior aspect so as not to interfere with the potential placement of a type I thyroplasty window. In fact, in recent cases we found it easier to completely outline the type I thyroplasty window, elevate the inner perichondrium, and depress the cartilage rectangle before placing sutures for the arytenoid adduction if both procedures were done concurrently. Suture placement in this manner will approximate the contraction vectors of the thyroarytenoid muscle (medial suture) and the lateral cricoarytenoid muscle.

After the sutures were passed posteriorly, the Keith needle was removed and the adduction sutures were individually placed through the muscular process of the arytenoid with a Lane threading needle. With acoustic auditory feedback as well as direct visual examination with an Olympus ENF P2 nasopharyngoscope and video monitor, the appropriate tension was applied to the nylon sutures to cause the desired rotation and adduction of the arytenoid cartilage. Once in the desired position, the two 4-0 nylon sutures were secured to each other along the anterior surface of the thyroid cartilage. The strap muscles were reapproximated and the skin wound was closed. The patients were given antibiotics for 1 week.

CASE REPORTS AND RESULTS

Each case of vocal cord paralysis involved a different combination of cause of the paralysis, final position of the paralyzed vocal fold, atrophy of the paralyzed vocal fold, bowing of the contralateral fold, compensation of the contralateral fold, and patient motivation and desires. Therefore, each case will be described individually. The results were evaluated through voice recording, video laryngoscopy, and stroboscopy.

Case 1. A 37-year-old man had aphonia due to left vocal fold paralysis resulting from removal of a left vagal neurilemmoma 3 months earlier. Via direct laryngoscopy, the left vocal fold was injected laterally with five clicks of Teflon, which brought the membranous vocal fold into good opposition in the midline. Postoperatively, the posterior glottis remained open and was responsible for persistent dysphonia. Three months later a left arytenoid adduction was performed. Afterward the voice was improved, and on physical examination the arytenoid was well medialized. With the combination of Teflon injection and arytenoid adduction, the aphonia was corrected, and objective assessment demonstrated normal values for jitter and shimmer[6-8] (Table 3).

Case 2. A 31-year-old woman had dysphonia secondary to left vocal fold paralysis after resection of a posterior mediastinal bronchogenic cyst and repair of the membranous portion of the trachea 5 months earlier. The left fold was widely abducted and higher than the right fold. There was no significant bowing or atrophy noted of the paralyzed vocal fold. Electromyography revealed no fibrillation potential. A left arytenoid adduction was performed. Postoperatively on examination there was better height similarity between the two vocal folds, with good closure of the glottis and no bowing of the vocal folds. Her voice was markedly improved, both subjectively and objectively, yet slightly raspy (Table 3).

Case 3. A 38-year-old man had aphonia related to right vocal fold paralysis after removal of a vagal neurilemmoma 9 months earlier. On examination, the right vocal fold was lateralized with a large interarytenoid gap. An arytenoid adduction was performed. The voice was noted to be improved but not perfect. Jitter was elevated and the SNR was low (Table 3). On examination the posterior glottis was now totally closed, yet there was marked bowing and atrophy of the membranous right vocal fold. Also noted was some slight overrotation of the arytenoid. To compensate for the bowing of the right vocal fold and weakness of the voice, the patient used a high-pitched voice with low amplitude. He was strongly motivated to improve his voice further, and 7 months after the arytenoid adduction a right Teflon injection via direct laryngoscopy was performed for slight bowing of the left vocal fold and marked bowing of the right vocal fold. The patient went into laryngospasm postoperatively and was emergently intubated. Findings on glottic examination were similar to preoperative ones, with apparent displacement of the Teflon during the reintubation. A right type I thyroplasty was then undertaken. During the operation, direct visualization of the larynx and voice assessment led to the conclusion that no further procedures were necessary. On postoperative follow-up evaluation there was noted to be good closure of the glottis, with only slight bowing of the left vocal fold. Objective evaluation of the voice revealed improvement of the severe dysphonia with the arytenoid adduction, and further benefit from the type I thyroplasty (Table 3).

Case 4. A 63-year-old woman had dysphonia secondary to left vocal fold paralysis. The cause of the vocal fold paralysis was never definitively iden-

TABLE 3. PREOPERATIVE AND POSTOPERATIVE OBJECTIVE VOICE ANALYSIS DATA

Case	*Status*	*F0 (Hz)*	*Jitter (%)*	*Shimmer (%)*	*SNR (dB)*
1	Preoperative	Aphon	Aphon	Aphon	Aphon
	After Teflon injection and arytenoid adduction	128.9	0.40	0.25	37.48
2	Preoperative	216.4	9.63	1.40	10.32
	After arytenoid adduction	218.3	1.50	0.77	22.25
3	Preoperative	Aphon	Aphon	Aphon	Aphon
	After arytenoid adduction	161.7	4.72	0.41	20.51
	After type I thyroplasty	127.2	0.45	0.35	28.41
4	Preoperative	235.5	3.77	0.88	17.65
	After arytenoid adduction	NC	NC	NC	NC
5	Preoperative	Aphon	Aphon	Aphon	Aphon
	After arytenoid adduction	135.3	6.34	1.78	15.50
6	Preoperative	163.1	4.94	5.72	11.93
	After arytenoid adduction	144.7	1.35	1.22	18.20
7	Preoperative	Aphon	Aphon	Aphon	Aphon
	After arytenoid adduction and type I thyroplasty	102.7	0.93	2.43	23.43
8	Preoperative	148.9	6.71	1.66	18.65
	After arytenoid adduction and type I thyroplasty	156.4	0.75	0.56	31.20
9	Preoperative	142.0	1.55	1.84	20.66
	After arytenoid adduction and type I thyroplasty	127.0	0.60	0.66	29.01
10	Preoperative	84.4	1.85	5.47	9.87
	After arytenoid adduction and type I thyroplasty	84.3	0.30	1.29	20.97
11	Preoperative	214.8	0.90	2.32	14.03
	After arytenoid adduction and type I thyroplasty	200.0	0.50	1.93	24.54
12	Preoperative	Aphon	Aphon	Aphon	Aphon
	After arytenoid adduction and type I thyroplasty	100.0	0.26	0.93	38.05

F0 — fundamental frequency, SNR — signal to noise ratio, Aphon — aphonic, NC — postoperative voice analysis not completed because of death of patient.

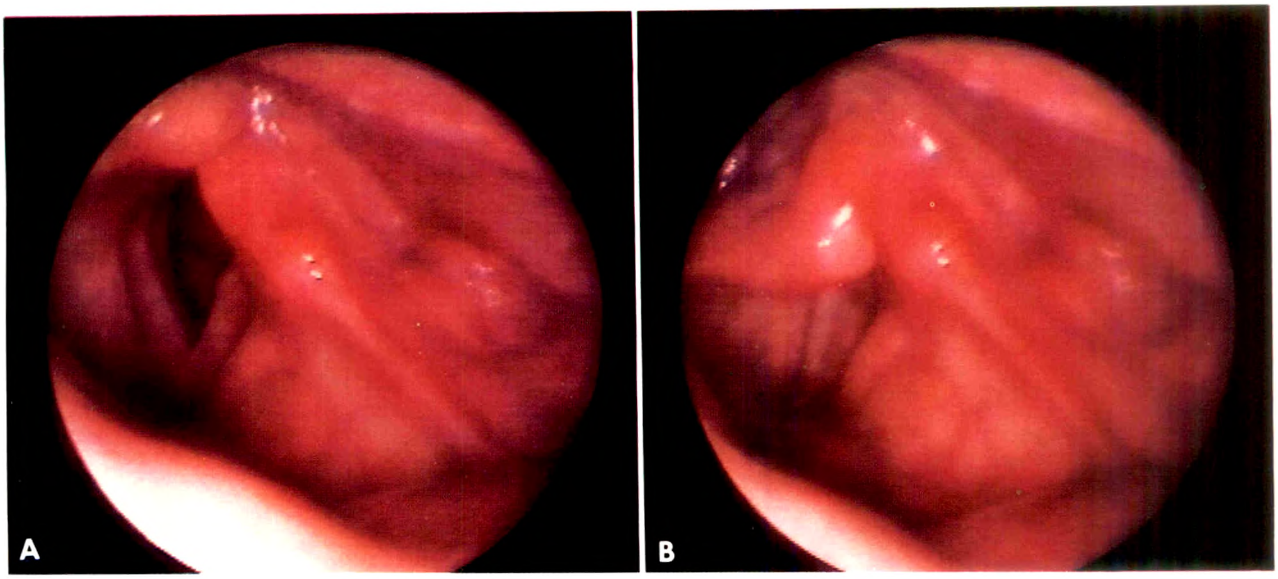
tified, yet it was felt to be secondary to viral infection. Examination revealed a large, incompetent posterior glottis. Six months after the diagnosis of the left vocal fold paralysis, the glottis was still noted to be widely patent posteriorly, and an arytenoid adduction was performed. Prior to the completion of postoperative voice analysis, the patient died of unrelated causes.

Case 5. A 71-year-old man had aphonia secondary to left vocal fold paralysis since repair of a ruptured thoracic aortic aneurysm 4 months before. There was a wide open posterior glottis. An arytenoid adduction was recommended along with the possibility of a type I thyroplasty, to be based on reevaluation during the surgical procedure. After only right arytenoid adduction, direct visualization of the glottis revealed good closure, and the voice had markedly improved, so a thyroplasty was not performed. Six months postoperatively the voice was slightly raspy, yet the patient was no longer aphonic. Objective assessment correlated with the subjective assessment of a raspy voice, with an elevated jitter and shimmer and a low SNR (Table 3).

Case 6. A 58-year-old man had dysphonia secondary to right vocal fold paralysis after resection of a glomus jugulare tumor 4 months earlier. The right vocal fold was positioned laterally, with a wide posterior gap and no significant atrophy of the membranous vocal fold. An arytenoid adduction alone was performed. Postoperatively, the voice was improved although not perfect, and objective assessment corresponded with the subjective observations (Table 3).

Case 7. A 62-year-old man had aphonia secondary to right vocal fold paralysis after resection of embryonal rhabdomyosarcoma in the right temporal, postauricular, retromandibular, infratemporal, and supraclavicular regions. There was also paralysis of the right pharyngeal muscles. Examination showed a large glottic chink. An arytenoid adduction and type I thyroplasty were performed along with a cricopharyngeal myotomy. Postoperative examination revealed normal jitter, shimmer, and SNR (Table 3).

Case 8. A 48-year-old woman had severe dysphonia secondary to left vocal cord paralysis since resection of vagal paraganglioma 12 months before. The left vocal cord was positioned laterally, with a wide glottic gap both anteriorly and posteriorly. An arytenoid adduction was performed and at the time of operation the vocal folds were still approximately 1.4 mm apart anteriorly after completion of the adduction procedure and closure of the posterior glottis. Therefore, in conjunction with the adduction procedure, a type I thyroplasty was performed on the left to close the anterior glottic defect. Postoperatively the voice was noted to be improved, with good closure of the entire glottis. Objective assessment revealed jitter and shimmer within the normal range and an increase in the SNR (Table 3).



(Case 12) Laryngoscopic views after arytenoid adduction and type I thyroplasty. A) During quiet respiration, showing medialization and correction of bowing of left vocal fold. B) During phonation, showing complete glottic closure.

Case 9. A 74-year-old man had dysphonia secondary to right vocal fold paralysis related to removal of a meningioma in the right jugular bulb, posterior cranial fossa, and upper jugular vein. The patient also had right palatal weakness and pharyngeal weakness along with dysphagia and aspiration. Laryngeal examination after removal of the tumor showed vocal fold paralysis with an open posterior glottis and an elevated paralyzed fold related to the high vagal paralysis. Marked atrophy of the right vocal fold was also noted. An arytenoid adduction was therefore planned to close the posterior glottis, along with a type I thyroplasty to compensate for the vocal fold atrophy. Postoperatively there was improved closure of the entire glottis, and objective assessment correlated with the subjective improvement of voice (Table 3).

Case 10. A 57-year-old man had dysphonia secondary to left vocal fold paralysis felt to be probably viral in origin. The patient also had a history of adenocarcinoma of the esophagus. There was a wide glottis, with the paralyzed left vocal fold positioned laterally and slightly higher than the right vocal fold. There was also significant bowing of the left vocal fold and slight bowing of the right vocal fold. A left arytenoid adduction along with a left type I thyroplasty was performed. Intraoperatively, it was felt that there was good closure of the glottis and that further procedures for the slight bowing of the right vocal fold were not indicated. After resolution of the edema, follow-up examination 4 months postoperatively revealed slight overrotation of the left arytenoid cartilage, with the vocal process protruding into the airway, and related bowing along the left membranous vocal fold producing a slight glottic gap. Objective as well as subjective assessment of the voice revealed improvement, although the voice was not perfect (Table 3).

Case 11. A 34-year-old woman had dysphonia secondary to a left vocal fold paralysis, felt to probably be viral. She had progressive weakness, hoarseness, and lowering of vocal pitch beginning over 1 year prior to evaluation and becoming constant in nature in the last 10 months. Magnetic resonance imaging scans were negative for disease. Electromyography showed left thyroarytenoid muscle paralysis. The left arytenoid was localized far laterally with a glottic chink. Slight atrophy and bowing of the left vocal fold was noted as well. A left arytenoid adduction was performed, and intraoperatively the voice was improved but still slightly breathy, so a type I thyroplasty was included. Evaluation 4 months postoperatively, after resolution of edema, revealed good glottic closure (Table 3).

Case 12. A 61-year-old man had aphonia due to a left vocal cord paralysis believed to be related to endotracheal intubation. Examination revealed marked atrophy and bowing of the left vocal fold as well as slight bowing of the right vocal fold. On phonation the posterior glottis remained open, with an interarytenoid distance of 3 mm. The left vocal fold also appeared slightly higher in position than the right vocal fold. An arytenoid adduction was performed in conjunction with a type I thyroplasty. At the time of operation there was good closure of the glottis. Postoperatively, all vocal measurements were normal (Table 3), and on examination there was complete glottic closure on phonation (see Figure).

DISCUSSION

Vocal fold Teflon injection and type I thyroplasty are usually successful in treating unilateral vocal fold paralysis with a closed or narrow posterior glottic chink.[2,3,11,12] However, in the presence of a lateralized paralyzed vocal fold and a large posterior glottic defect, neither a Teflon injection nor type I thyroplasty alone is able to achieve a relatively normal voice postoperatively. Teflon injection cannot be used successfully to medialize the arytenoid cartilage, and because the cricoid cartilage overlaps the thyroid cartilage posteriorly, inward displacement of a type I thyroplasty thyroid cartilage window posteriorly cannot be performed to effectively close this glottic area without violating the inner thyroid perichondrium. The first case described illustrates the inability of an anterior medialization procedure alone to correct for a vocal fold paralysis with a wide glottic defect that includes the interarytenoid space. Arytenoid adduction is a procedure that specifically is indicated for the correction of a wide posterior glottic chink. Arytenoid adduction also has the capability of correcting a difference in the levels of the true vocal folds by lowering the paralyzed vocal fold.

Although the arytenoid adduction procedure can close the posterior glottis and lower the paralyzed vocal fold to correct a height difference, this procedure alone is often unsuccessful in fully rehabilitating the voice, specifically because it does not directly affect the anterior vocal fold. In conjunction with an arytenoid adduction, a Teflon injection or type I thyroplasty is often indicated to medialize the membranous paralyzed vocal fold further. This is particularly of value in cases of marked atrophy and bowing of the membranous portion. In the case of the patient suffering from presbylaryngis and senile bowing of the vocal folds, a type I thyroplasty of the contralateral vocal fold may also be indicated to correct the bowing of the nonparalyzed side.

Case 3 demonstrates the inability of an arytenoid adduction alone to correct a lateralized paralyzed vocal fold with marked atrophy and bowing. Furthermore, in cases 5 and 6, a type I thyroplasty in conjunction with the arytenoid adduction would probably have been beneficial. In both cases 5 and 6 the vocal fold paralysis was only 4 months old, and further atrophy of the vocalis muscle likely occurred postoperatively. Currently our technique is to initially perform an arytenoid adduction in those patients with vocal fold paralysis and a lateralized fold. We assess the immediate results intraoperatively, with the option to proceed with a type I thyroplasty as indicated. The use of local anesthesia with intravenous sedation allows for intraoperative assessment of the voice and direct visualization of the larynx during phonation.

Although there were no major complications in our cases and the quality of the voice was always improved, a perfect voice was not always obtained. The arytenoid adduction procedure is technically a more difficult procedure to perform. In two of the cases (cases 3 and 8) there was slight overrotation of the arytenoid cartilage, the most common complication of this procedure. This caused the vocal process to protrude into the glottis with associated bowing of the membranous vocal cord. Overrotation and too much medial shift of the vocal fold across the midline can be caused by excessive traction on the sutures attached to the muscular process of the arytenoid. Placement of a suture through the muscular process of the arytenoid in an extreme lateral position can also lead to overrotation. If the arytenoid is rotated too much, a rough and "pressed" voice often results, and a type I and type IV thyroplasty may help correct this condition.[2] Another complication associated with arytenoid adduction was shortening of the vocal fold (case 3). This was probably related to excessive opening of the cricoarytenoid joint posteriorly and subsequent forward displacement of the arytenoid cartilage with traction on the suture through the muscular process.

One of the greatest difficulties with laryngeal framework surgery continues to be the difficulty with intraoperative assessment and the ability to predict the long-term postoperative results. The swelling and edema of the larynx that occurs during the surgical manipulation needs to be taken into consideration when establishing the new position of the vocal folds. One must therefore overcorrect intraoperatively and achieve a slightly tight or pressed voice, taking into account the edema that will resolve postoperatively. Other factors affecting the long-term postoperative result are related to the healing process. In the case of immediate treatment of a vocal fold paralysis, further atrophy will affect the long-term postoperative result. The longevity of the vocal fold tension created by the adduction of the arytenoid is also uncertain. Finally, modification of an artyenoid adduction without direct surgical intervention of the vocal fold may be difficult because of the ankylosis that occurs at the opened cricoarytenoid joint.

SUMMARY

The arytenoid adduction procedure is a surgical technique that provides the otolaryngologist with an effective means for correcting large posterior glottic defects. The arytenoid adduction procedure is a technically challenging procedure related to the identification of the muscular process of the arytenoid and appropriate positioning with rotation of the arytenoid cartilage. The use of an anterior medialization procedure such as a type I thyroplasty is a valuable adjunctive procedure in those cases of concurrent marked anterior vocal fold bowing. Every case of vocal fold paralysis is unique, and one must remember that patients with vocal fold paralysis can have different glottic configurations and vocal results. Likewise, there is not one universal treatment for vocal fold paralysis and each patient must be evaluated carefully to determine the appropriate procedure or combination of procedures. In the case of the open posterior glottis, the arytenoid

adduction procedure has proven to be an effective and reliable treatment for this troublesome defect.

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The First International Skull Base Congress will be held June 14-20, 1992, in Hanover, Germany. For further information, contact Madjid Samii, MD, Professor and Chairman of Neurosurgery, Medical School Hanover, Neurosurgical Clinic, Hospital Nordstadt, Haltenhoffstr 41, D-3000 Hanover 1, Germany; phone 0049-(0)511-7638245 or 623151, fax 0049-(0)511-7638606.

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MAURICE H. COTTLE HONOR AWARD

The American Rhinologic Society wishes to announce the competition for the Maurice H. Cottle Honor Award. The manuscript submitted should represent basic or clinical rhinologic research. The winner of the competition will receive a check for $1,000 and will be requested to present the winning manuscript at the 38th annual scientific meeting, which will be held on Saturday, September 12, 1992, in Washington, DC. Submit manuscript by June 1, 1992, to Dr George Facer, Secretary, American Rhinologic Society, 200 First Street SW, Rochester, MN 55905.

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COLLAGEN IN THE DEVELOPING LARYNX

PRELIMINARY STUDY

SEYMOUR R. COHEN, MS, MD
LOS ANGELES, CALIFORNIA

DAVID T. CHEUNG, PHD
LOS ANGELES, CALIFORNIA

MARCEL E. NIMNI, PHD
LOS ANGELES, CALIFORNIA

VLADIMIR MAHNOVSKI, MD
LOS ANGELES, CALIFORNIA

GRACE LIAN, MD
LOS ANGELES, CALIFORNIA

NATASHA PERELMAN
LOS ANGELES, CALIFORNIA

ALFONZO P. CARRANZA, MD
SAN JOSE, COSTA RICA

The primary purpose of this study was to determine the types of collagen in the developing human larynx that contribute to the structural framework and function of various components of this organ. The infant larynx is much more than a mere miniature of the adult "voice box." There are many age-related differences that occur in the larynx from the newborn period to the adult period of life. While collagen has been studied in numerous tissues, both normal and diseased, there have been no studies of the whole organ content, types, and/or changes of collagen in the developing human larynx that may account for many of the clinical findings. This study may at least in part explain whether collagen differences may account for the structural changes and responses that are seen in clinical practice.

KEY WORDS — cartilage, collagen, connective tissue, development, larynx.

INTRODUCTION

The cellular histology of the adult human larynx has been well documented. Greater interest has been shown in the epithelial structures than in the other laryngeal connective tissues. Little has been reported regarding the biochemistry of the supporting laryngeal cartilaginous and soft tissue framework. Further, little has been written about the biochemical changes in these tissues during the growth and development of the larynx.

There is a paucity of knowledge about the true cause of changes in the response of the infant larynx to trauma and disease as compared to the changes found in the maturing larynx. Still remaining to be explained is why these responses subside and why an anomaly such as laryngomalacia reverts to normal with growth and development.

The purpose of this preliminary study is to evaluate the collagen content of selected cartilages of the normal developing human laryngeal framework as to type and quantity. An understanding of the normal biochemical makeup of laryngeal connective tissue may be essential in order to prevent and treat the devastating effects of trauma and other diseases on the larynx.

Collagen is extremely important in the growth, development, repair, regeneration, and structural integrity of the laryngeal framework. Collagen is very distinctive in that it forms insoluble fibers with a very high tensile strength. It is the most common and abundant mammalian protein and accounts for 30% of all proteins in the body.[1]

The term collagen is derived from Greek words meaning "to produce glue," and collagen is present in all organs of the body. It serves as a scaffolding that holds cells together. Connective tissues form the architectural framework of the vertebrate body. As a major fibrous element of skin, bone, cartilage, blood vessels, and teeth, collagen has been extensively studied. However, whole organ studies have not been common and there are no studies reported of this connective tissue element in the larynx, which depends upon this protein substance for the integrity of its cartilaginous framework. The high tensile strength of most organs (eg, skin) is due to the presence of collagen, a fibrous protein.

Histologically, cartilages of the larynx have been determined to be hyaline, except for the epiglottis, which is elastic fibrocartilage.

In the last two decades it has become apparent that not all collagen molecules are alike. Type II collagen, which is the sole component of hyaline cartilage, was

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From the Departments of Otolaryngology (Cohen) and Pathology (Mahnovski), Children's Hospital of Los Angeles, and the Departments of Biochemistry (Cheung, Nimni, Lian, Perelman) and Pathology (Mahnovski), University of Southern California, Los Angeles, California, and the Department of Pathology, National Children's Hospital, San Jose, Costa Rica (Carranza). This research was funded by a grant from the Seymour R. and Odelia A. Cohen Medical Foundation.

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REPRINTS — Seymour R. Cohen, MS, MD, 4301 Cromwell Ave, Los Angeles, CA 90027.

the first tissue-specific collagen to be described. In contrast to the more ubiquitous type I collagen, present in bone, skin, and most organs, it contains three identical polypeptide chains that are highly glycosylated. Since then, around 14 different types of collagens have been described in human tissues. Fibrocartilage, in contrast with hyaline cartilage, contains type I collagen.

BIOCHEMISTRY OF COLLAGEN

One of the functions of protein is its structural role.[1,2] Since disease is associated with excessive accumulation of collagen leading to various forms of fibrosis, an understanding of the normal collagen content and typing is essential.

Each collagen seems to have a specific purpose, although this has not yet been completely elucidated. The extracellular matrix was thought to serve mainly as a relatively inert scaffolding that stabilizes the physical structure of tissues. It is now clear that the matrix plays a more active and complex role in regulating the behavior of the cells that contact it.[3,4] The extracellular matrix is composed primarily of fibrous proteins embedded in a hydrated polysaccharide gel. In most connective tissues these macromolecules are secreted largely by fibroblasts. There are two more classes of extracellular macromolecules that make up the matrix: 1) polysaccharide glycosaminoglycans and 2) fibrous proteins. Of the proteins, collagen and elastin are mainly structural, and fibronectic and laminin are mainly adhesive.[2-4] This study deals only with collagen, the major protein of the extracellular matrix.

Collagen is a family of highly characteristic fibrous proteins found in all multicellular animals.[1,3,4] The collagen molecules are stiff, triple-stranded helical structures. Three collagen polypeptide chains called α chains (each about 1,000 amino acids long) are wound around one another in a regular superhelix to generate a ropelike collagen molecule about 300 nm long and 1.5 nm in diameter. The collagens are rich in proline, hydroxyproline, and glycine, which are very important in the formation of a triple-stranded helix. Glycine is the smallest amino acid, regularly spaced at every third residue. Proline and hydroxyproline, because of their ring structures, stabilize a left-handed helical conformation in each α chain, with three amino acid residues per turn. Throughout the central region of the α chain, proline allows the three helical α chains to pack tightly together to form the final collagen superhelix.

As mentioned, many distinct collagen α chains have been identified, each encoded by a separate gene. Different combinations of these genes are expressed in different tissues. To date, about 14 types of collagen have been recognized, each a distinct protein product from one or more genes.[3,4] The best-defined of the collagen types and the most relevant to these studies are types I, II, III, and IV.

Types I, II, and III are the fibrillar collagens and are the main types found in connective tissue. Type I collagen is the most common by far and is found in skin, tendon, bone, ligaments, cornea, and internal organs. It comprises about 90% of body collagen. Type II collagen is found in hyaline cartilage, the intervertebral disc, the notochord, and the vitreous body of the eye. Type III collagen is found in skin, blood vessels, and internal organs. Type IV collagen (a nonfibrillar type) is found in the basal lamina. It is important that the organization of collagen fibrils in the extracellular matrix is adapted to the needs of the tissue.[2]

TYPES OF COLLAGEN

Type I collagen is the most prevalent type in the vertebrate organism. The major molecular species of type I collagen is a heterotrimer consisting of two identical $\alpha1$ chains and a simple $\alpha2$ chain. Electron immunohistochemical localization of type I collagen in a variety of tissues typically shows cross-banded fibers with an average diameter of 40 to 60 nm and characteristic cross banding at 67-nm intervals. Type I collagen is often found associated with other types of collagen (types III, V, and VI), as well as other noncollagenous proteins in several major noncartilaginous connective tissues.[5]

Type II collagen is the cartilaginous counterpart to type I collagen and is the predominant collagen found in hyaline cartilage. The type II collagen molecule is a homotrimer consisting of three α chains. The type II collagen molecule interacts with other cartilage proteins (proteoglycans, structural glycoproteins, and type IX, X, and XI collagens) to form the cartilage matrix. Type II collagen also forms fibrous elements in other tissues such as the notocord, the nucleus pulposus, and the vitreous humor of the eye.[5]

Type III collagen is found in association with larger type I fibers in the more distensible connective tissues such as the dermis and arteries.

Type IV collagen is localized to all basement membranes and is known as the basement membrane collagen. Aggregates of this type of collagen form a loose network, rather than fibers, because of the presence of nonhelical domains.

MATERIALS AND METHODS

Tritium-labeled sodium borohydride (^3H-$NaBH4$;

9.5 Ci/mmol) was purchased from Amersham (Arlington Heights, Ill), and sequenal grade dimethylformamide was purchased from Pierce Chemical Co (Rockford, Ill).

Selection and Identification of Tissue Samples. Whole organ autopsy specimens of the larynx were collected, including, whenever available, portions of the body of the hyoid and the attached upper three tracheal rings. The specimen was wrapped to prevent potential drying and immediately frozen and stored at -70°C. The age of the patient at the time of death, regardless of cause, was documented. After defrosting, the specimens were immediately and carefully dissected to remove all external musculature so as to anatomically outline the cartilaginous framework of the larynx, and in some instances the hyoid and upper tracheal cartilages. Each structure was then sampled for biopsy: a sliver of cartilage was removed and immediately placed into a vial containing chloroform-methanol (50/50, vol/vol), and the specimens were refrigerated at temperatures of 2°C to 6°C pending transfer to the biochemical laboratory. In each specimen the sliver of cartilage was obtained as follows.

1. From the epiglottis at its superior tip by a transverse cut.
2. From the thyroid lamina at its most lateral margin.
3. From the cricoid by a sliver taken from the lamina.
4. From the arytenoid by removing a portion of its muscular process.

The remaining structures — the trachea, true vocal cord, false vocal cord, and center of the body of the hyoid — were all stored for further studies.

Preparation of Tissues. The tissues (10 to 20 mg wet weight) were extracted with chloroform-methanol (50/50, vol/vol) to remove fat. The tissues were then washed with methanol to remove the chloroform, and saline was used to remove the methanol. The tissues were then extracted with 4 mol/L guanidine to remove proteoglycans. The extracted tissues, consisting mainly of collagen, were then washed with saline to remove the guanidine before cyanogen bromide (CNBr) digestion.

CNBr Digestion. The procedure used was that of Miller.[6] Samples (10 mg wet weight) were digested in 0.8 mL of nitrogen-purged formic acid containing 40 mg CNBr for 4 hours at 30°C. The mixtures were diluted tenfold with water by volume and lyophilized twice at the end of the digestion to remove excess CNBr.

^{3}H-NaBH4/Dimethylformamide Labeling of CNBr Peptides. The method used to label proteins with ^{3}H by methylation of amino acid groups was modified by a procedure previously described by Cheung et al.[7] The CNBr derived from defatted tissues or purified collagen preparation (25 mg dry weight) was lyophilized to dryness and suspended in 0.2 to 0.5 mL of sequenal-grade dimethylformamide. A 0.02-mL aliquot of ^{3}H-NaBH4 (100 mCi/mL, in dimethylformamide) was added to each sample, which was vigorously mixed and then allowed to stand for 2 hours. The labeling reaction was terminated by adding 0.5 mL of 0.5 mol/L acetic acid. The free label was removed by desalting on a Bio-gel P-2 column with 0.1 mol/L acetic acid (column volume, 30 mL; fraction volume, 0.5 mL). The void volume peak containing radioactive peptides was collected and lyophilized.

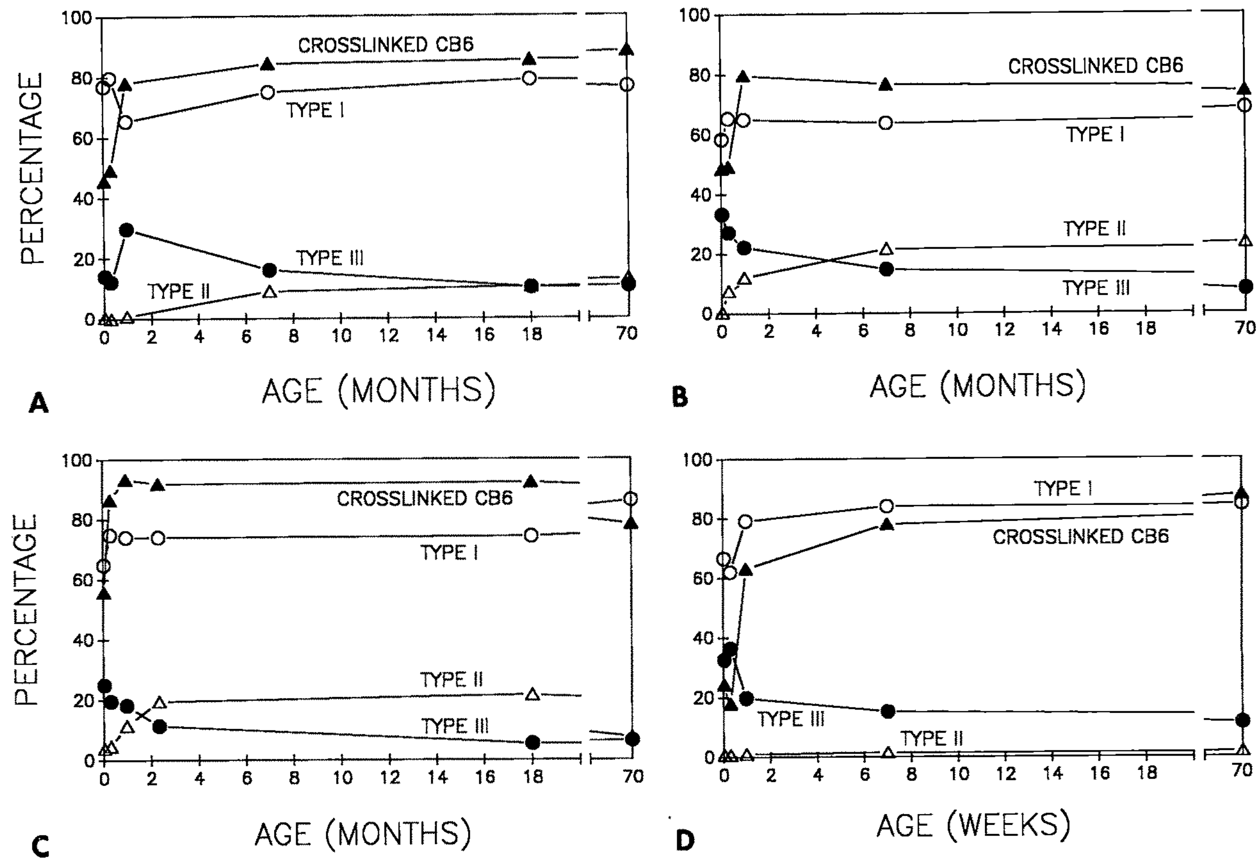
Mercaptoethanol Reduction of CNBr Peptides and Second CNBr Digestion. Radioactively labeled CNBr peptides were subjected to overnight reduction at 55°C in the presence of 25% mercaptoethanol in 0.1 mol/L ammonium carbonate. Samples were then diluted with a fourfold volume of water (final mercaptoethanol concentration, 5%). The mercaptoethanol was then removed by desalting the diluted samples on a P-2 column as described above.

2-D Isoelectric Focusing and NaDodSO4 Electrophoresis Mapping of ^{3}H-NaBH4 CNBr Peptides. The technique was described by Benya.[8] The CNBr peptide samples that were dissolved in urea and amphiline containing sample buffer were subjected to isoelectric focusing in polyacrylamide focusing tube gels. The first dimensional gel was then removed from the tube and cast on top of the second dimensional slab gel and electrophoresed in the presence of sodium dodecosulfate. The resulting maps were either stained with a copper sulfate containing Coomassie blue and then destained with 35% methanol, or processed for fluorography.[8]

Quantitative Analysis of Fluorographs From Two-Dimensional Maps. Some x-ray films were preexposed to yield a background of 0.15 optical density at 600 nm after being developed. These films were then exposed to processed two-dimensional (2-D) maps for various lengths of time at -70°C. The films were developed in a Kodak X-omatic developer and then scanned on a Bioimage Visage-60 2-D densitometer-integrator.

RESULTS

We analyzed the distributions of type I, II, and III collagens by 2-D CNBr peptide mapping in the thyroid lamina, cricoid cartilage, arytenoid, and epiglottis of the developing larynges obtained at autopsy from subjects 1 day, 9 days, 1 month, 7 months, 18



Distributions of collagen types and collagen cross-linking at ages studied. A) Epiglottis. B) Cricoid cartilage. C) Thyroid lamina. D) Arytenoid.

months, and 70 months old. The degree of collagen cross-linking was also analyzed by measuring the amount of non–cross-linked type I C-terminal CNBr peptide α1-CB6 in each sample.

Epiglottis. The changes of the distributions of type I, II, and III collagens during early development in this tissue are shown in the Figure, A. Type I, a major collagen type in most connective tissues except cartilages, was found to be the major type of collagen in the epiglottis at birth, and this percentage was maintained at levels of 70% and 80% throughout the first 70 months of life. Type II collagen, the major collagen type found in articular and hyaline cartilage, was absent in the epiglottis at birth. This collagen (type II) first appeared at 1 month of age and gradually increased to about 12% at 70 months of age. At birth, type III collagen (a type present in higher amounts in fetal as well as vascular tissues) was present in levels of 15%, but increased to about 30%, following which it gradually diminished to about 10% at 70 months of age. At birth, approximately 45% of type I α1 chains were cross-linked at the C-terminal end, since only 55% of the free peptide was observed in the 2-D maps. Cross-linking increased rapidly after birth, and about 80% of the α1 chains were cross-linked after 1 month of age.

Cricoid Cartilage. Distributions of type I, II, and III collagens in the cricoid cartilage from specimens at the various ages studied are shown in the Figure, B. Type I collagen was also found to be the major collagen type (between 60% ad 65%) from 1 day to 70 months, but at a lower level than that found in the epiglottis. At birth, type II collagen was absent and there was about 34% of type III collagen. Type II collagen appeared soon after birth (7.5% at 9 days of age) and increased rapidly during the first month, after which it reached 21.6% at 7 months of age. Type III collagen was present at levels of 33% at birth in this tissue, but decreased rapidly to 22% at 1 month of age. This percentage continued to drop to 10% at 70 months of age. The rapid loss of α1-CB6 of type I collagen in this tissue also indicates that cross-linking of collagen occurs quickly after birth.

Thyroid Lamina. The distributions of type I, II, and III collagens in the thyroid lamina during early development are shown in the Figure, C. Type I collagen was, again, found to be the major collagen type, with increases from 64% to 84% throughout the early neonatal development of the thyroid lamina. Type II collagen was present at a very low level (4%) at birth, but increased to about 20% at 2 months of age. This level was maintained until 18 months of age, but dropped to about 8% at 70 months of age. Type III collagen decreased from 25% at birth to 7% at 7 months of age. Cross-linking of collagen was also found to occur rapidly during the first month of life.

Arytenoid. The changes in distributions of type I, II, and III collagens in the arytenoid during the early development of the larynx are shown in the Figure, D. Unlike the other tissues described above, type II collagen was not found in the arytenoid from birth to 70 months of age. However, type I collagen increased from 65% to 80% during the first month of life and was maintained at this level up to the age of 70 months. Type III collagen was present at birth at levels of 35%, decreased to 20% rapidly during the first month of age, and continued to drop to 12% at 70 months of age. Cross-linking of collagen was also found to occur rapidly during the first month of life in this tissue.

SUMMARY

Type I collagen was the major component found in all four cartilaginous structures analyzed. However, a small percentage of type II collagen was found in the thyroid lamina. Type II collagen was absent at birth in all laryngeal cartilages analyzed. Type III collagen was found in concentrations of 15% to 35% in all of the laryngeal cartilages at birth. It is also evident that significant amounts of collagen are already cross-linked at birth.

A dynamic change in the distribution of the different types of collagen and an increase of cross-linking of type I collagen occur within the first month of life in all four components of the larynx analyzed. Cross-linking is a part of the maturation process of collagen and is very important to the stability and mechanical properties of the collagenous tissues. No significant amount of type II collagen is present in the arytenoid cartilage. While type II collagen increases in concentration to 20% in both the cricoid cartilage and the thyroid lamina at 7 months of age, it was found to remain at this level in the cricoid cartilage for up to 70 months of age. However, type II collagen drops to 8% within the thyroid lamina. Type III collagen decreases to levels below 10% as the larynx passes its neonatal development.

CONCLUSIONS

This preliminary study establishes the types and quantities of fibrillar collagens present during the early growth and development of the laryngeal cartilaginous framework. The study does not attempt to correlate these findings with any clinical aspects of laryngeal disease. It is obvious from these studies that collagen is in a constant state of flux during laryngeal growth and development.

In progress are studies that will include information regarding 1) sex variations, if any; 2) hormonal changes at puberty; 3) trauma; 4) infection; 5) congenital anomalies; 6) autoimmune disease; 7) the aging process; and 8) tissue distribution and localization by using immunohistochemical methods.

Also in progress and soon to be completed are evaluations of the collagen content of the tracheal rings, hyoid bone, true vocal cords, false vocal cords, and the aryepiglottic folds. Also in progress are electron microscopy and immunochemistry studies.

Histologically, the laryngeal cartilages are considered hyaline-type cartilage, yet biochemically these cartilages do not have the type II collagen commonly associated with this type of cartilage.

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FREE JEJUNAL GRAFT: EFFECTS OF LONGITUDINAL MYOTOMY

BRUCE H. HAUGHEY, MBCHB, FRACS JAMES W. FORSEN, MD
ST LOUIS, MISSOURI

Pharyngoesophageal reconstruction using the free vascularized jejunal graft results in dysphagia in approximately 20% to 40% of patients. This may be caused by graft contractility, and we therefore developed this canine model to assess the functional effects of myotomy on transplanted jejunum. Nine female dogs underwent microvascular transposition of jejunum to the neck, the bowel being placed subcutaneously with two end jejunostomies. Baseline functional manometry was performed. Five animals then underwent complete longitudinal myotomy and four animals underwent a sham procedure. Graft function was then reevaluated after complete wound healing. Contraction frequency, contraction amplitude, and total work done by the graft were recorded; all grafts demonstrated activity and were more active postrecovery than at the time of operation. Although myotomy animals showed a within-group trend to decreased contractility postintervention, this was not statistically significant. Furthermore, there was no significant postintervention difference between the sham and myotomy groups. We conclude that our model is effective for the study of activity in the free jejunal graft and that longitudinal myotomy does not significantly reduce, let alone ablate contraction.

KEY WORDS — free vascularized jejunal graft, graft contractility, myotomy, pharyngoesophageal reconstruction.

INTRODUCTION

Reconstruction of the upper aerodigestive tract after ablative procedures has always been of major concern to head and neck surgeons. Skin and musculocutaneous flaps have been used extensively,[1-3] because they are readily available, and patients can reestablish oral nutrition by using gravity through a passive conduit. These methods result in an adynamic segment in the swallowing tract with minimal adaptation to the functional qualities of either pharyngoesophageal musculature or the mucosal lining.

Improvement in reconstruction of pharyngoesophageal defects has accompanied the use of enteric tissue. Donor sites have included stomach, jejunum, ileum, and colon, and reliability of microvascular technique has made the use of free jejunal tissue transfer popular. The idea, however, of free tissue reconstruction in this region is not new. In 1907, Carrel[4] reported the experimental free transfer of bowel for restoration of an esophageal defect. Hiebert and Cumings[5] were the first to report this method in humans in 1961, using gastric antrum.

The free jejunal graft has been demonstrated to provide very satisfactory upper aerodigestive tract reconstruction. Advantages include relative ease of harvest, low donor site morbidity, a lumen diameter compatible with that of the esophagus, and lubrication of orogastric transport with constant secretion from the mucosal glands. Although the use of free jejunal grafts is widespread,[6] problems have been identified. Approximately 40% of patients have some degree of delay in bolus transit time through the grafted segment.[7] This is potentially an even greater problem if the larynx is preserved, as has been reported in conjunction with the use of free jejunal grafts,[8] because of the ever-attendant risk of aspiration. The motility problems in these grafts seem to be due to continued, unmodulated peristalsis and segmental contractions mediated by the myenteric plexus. Although the grafts are extrinsically denervated, these autonomous plexi continue to function. Disuse atrophy of muscle is thereby prevented and an associated decrease in activity may not ensue.

One of us (B.H.H.) developed a canine model that allowed for assessment of free jejunal graft motility characteristics.[9] By placing the segment subcutaneously in the neck and exteriorizing it to form end jejunostomies, easy access was provided to the lumen. Subsequently, various baseline studies were performed, including manometry, fluoroscopy, and electromyography.[10]

The present study was designed to eliminate the intrinsic contractions seen in the canine free jejunal graft. Specifically, a longitudinal myotomy was performed to convert the graft into a passive yet mucosally lined conduit. In addition, the original model[9] was modified so that it could be tested over a longer period of time.

From the Department of Otolaryngology–Head and Neck Surgery, Jewish Hospital Division, Washington University School of Medicine, St Louis, Missouri. Supported by a Jewish Hospital of St Louis Research Endowment Grant, 1990. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Committee on the Humane Care of Laboratory Animals (CHCLA) of Washington University.

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REPRINTS — Bruce H. Haughey, MBChB, FRACS, Dept of Otolaryngology–Head and Neck Surgery, Washington University School of Medicine, 4932 Forest Park Blvd, St Louis, MO 63108.

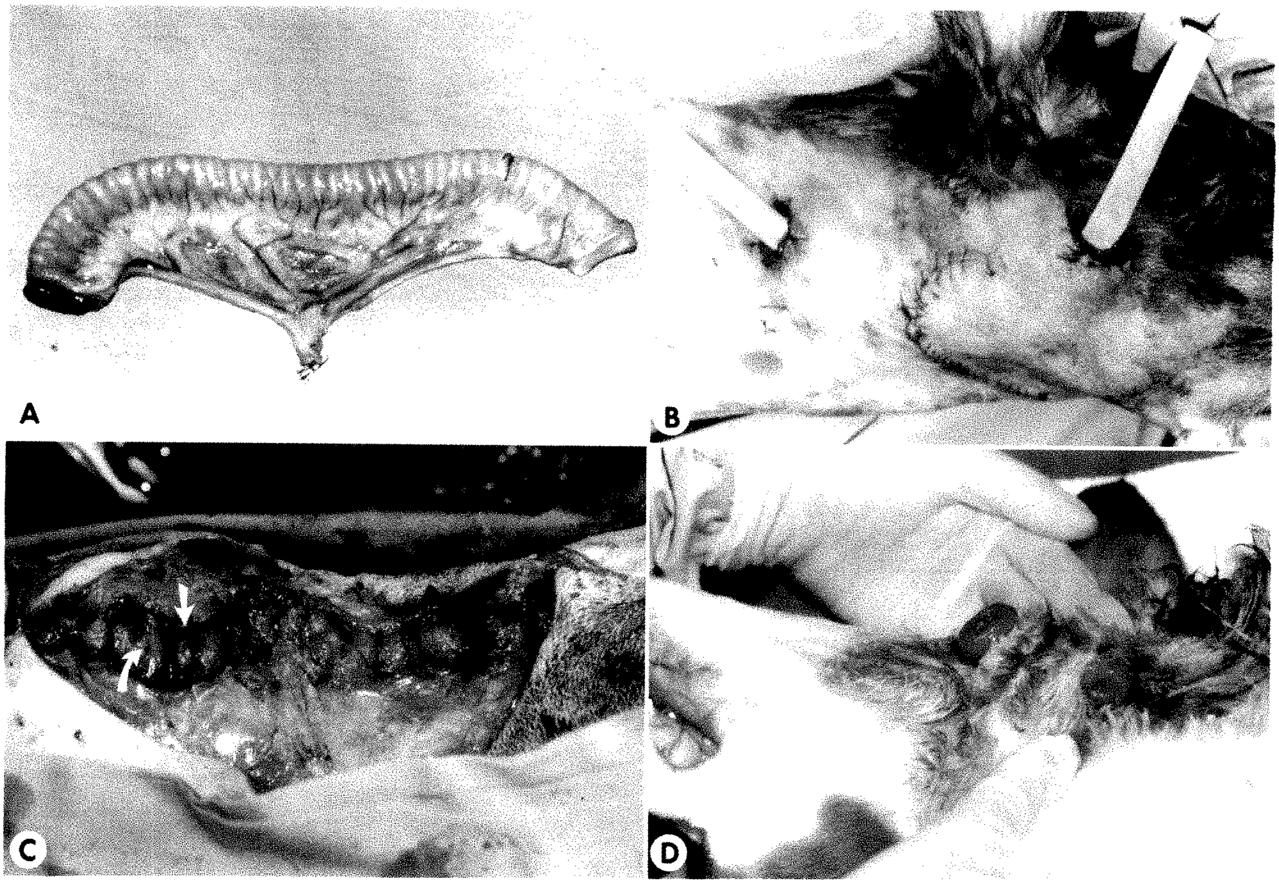

Fig 1. Photographs from myotomy procedure. A) Canine free jejunal graft (20 cm). B) Revascularized jejunal graft with Penrose drain exiting from jejunostomies. C) Myotomized free jejunal graft. Note exposed submucosa (curved arrow) and cut muscle margin (straight arrow). D) Free jejunal graft in ventral neck position. Note herniation of graft at jejunostomies and shortening of subcutaneous segment.

MATERIALS AND METHODS

The present study modified an earlier technique, in which we developed a canine model for study of revascularized free jejunal segments.[9] The modified incisions and graft placements detailed below allowed longer-term analysis of the canine free jejunal graft in both the control and experimental myotomy arms.

Nine female mongrel dogs were used, weighing between 15 and 20 kg. They received 1 g of neomycin sulfate orally twice a day for 2 days and were given nothing to eat for 24 hours preoperatively. On the day of operation, they were sedated with 10 mg of acepromazine maleate administered intramuscularly, and then shaved. Anesthetic induction was achieved with 25 mg/kg sodium pentobarbital administered intravenously and was followed by endotracheal intubation and maintenance on halothane 1%, nitrous oxide 1 L/min, and oxygen 1 L/min. After preparation, separate operative fields were established in the neck and abdomen.

A midline laparotomy was performed and jejunum just distal to the ligament of Treitz was evaluated. A bowel segment measuring from 15 to 25 cm, served by a single artery and vein, was harvested (Fig 1A), and the intestinal lumen was flushed with an iodine solution. The segmental artery and vein were prepared under the microscope, while the graft was bathed in cold saline. Bowel continuity in the abdomen was then reestablished by using a single layer of interrupted 3-0 Vicryl suture. The abdominal wall was closed in the standard layered fashion.

A single curved neck incision was then made, approximately 12 cm in length and transverse to the long axis of the neck and the jejunal graft. This approach was designed to minimize scar contracture along the axis of the graft. This in turn prevented gross shortening and herniation of the graft during the study period. This approach was a revision of our original model,[9] which employed a longitudinally directed neck incision. The external jugular vein, its major tributaries, and the lingual artery were carefully dissected free. End-to-end anastomoses were established between recipient and donor vessels by using interrupted or continuous 10-0 nylon suture and standard microvascular technique. Once the graft

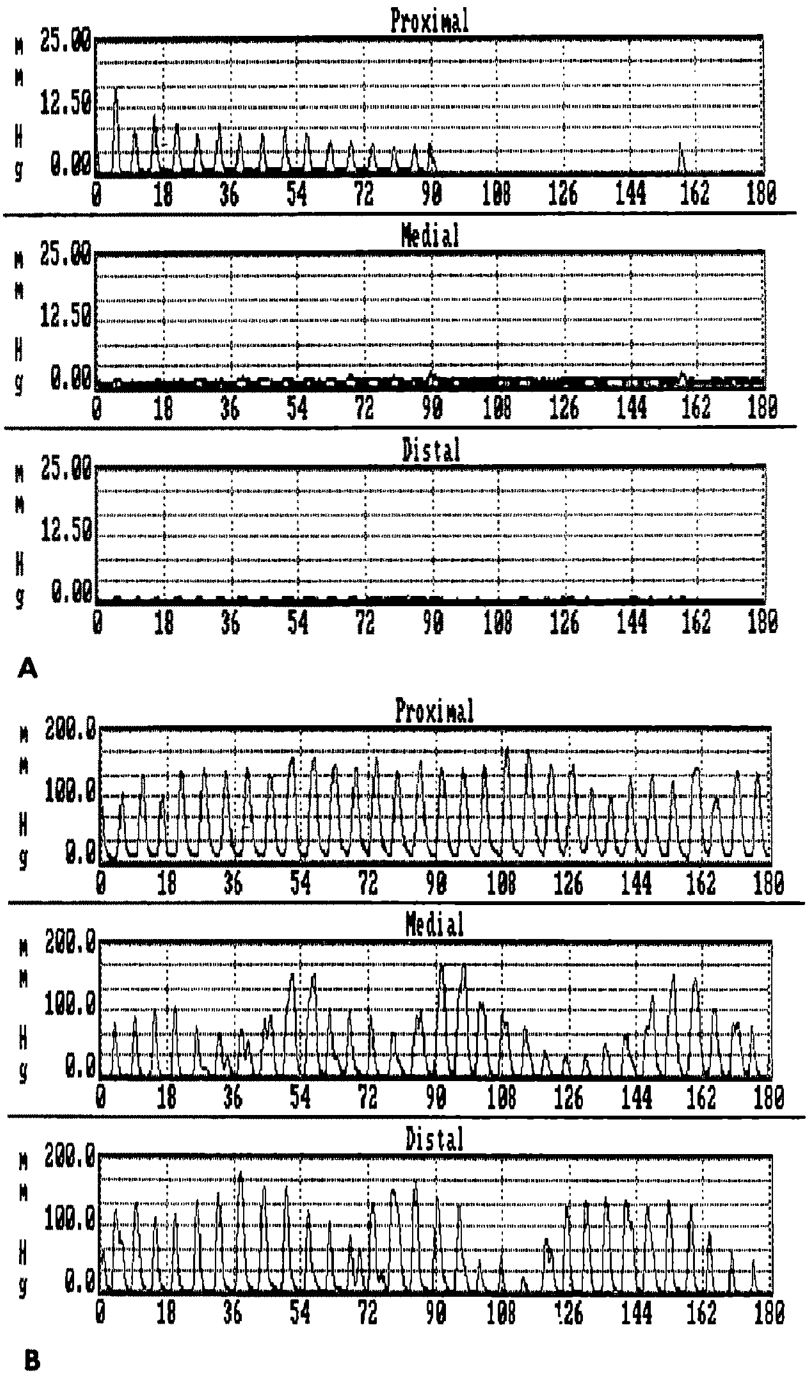

Fig 2. Representative manometry tracings from three transducer probes (time in seconds). A) At baseline. B) After metoclopramide hydrochloride stimulation.

was being perfused, it was placed parallel to the long axis of the neck in a lateral subcutaneous pocket. This dorsolateral placement kept the graft out of the loosest ventral skin on the flexor aspect of the neck, again to minimize any shortening. The ends of the graft were then tunneled beneath the skin flaps, and end jejunostomies were fashioned. One Penrose drain was placed in the wound while another was inserted through the lumen of the graft to allow adequate drainage of jejunal secretions (Fig 1B). The neck wound was closed in a layered fashion and a mild pressure dressing using an orthopedic stocking was applied.

The animals received morphine intramuscularly perioperatively and 300 mg ampicillin sodium intramuscularly twice a day for 1 week. They were initially given water ad libitum and then fed canned food on the fourth postoperative day. They were later advanced to dry chow.

Evaluation of jejunal graft activity was achieved with solid state manometry. The manometry catheter housed three circumferential pressure transducers spaced 3.5 cm apart (Konigsberg Instruments) and

FREE JEJUNAL GRAFT MOTILITY

Condition	*Parameter*	*Intervention*	*n*	*Testing Period (mean ± SD)* *Time of Operation*	*Postrecovery and Preintervention*	*Postintervention*
Baseline	Contractions per minute	Sham	4	1.5 ± 1.1	0.5 ± 0.7	3.4 ± 1.8
		Myotomy	5	1.3 ± 1.2	4.3 ± 3.5	3.1 ± 3.4
	Contraction amplitude (mm Hg)	Sham	4	7.7 ± 1.7	2.3 ± 2.5	7.8 ± 5.0
		Myotomy	5	11.6 ± 10.3	15.4 ± 15.0	11.6 ± 15.1
	Cumulative pressure (mm Hg/s)	Sham	4	115.0 ± 68.4	58.2 ± 31.9	226.8 ± 202.0
		Myotomy	5	131.9 ± 118.7	249.7 ± 237.6	199.5 ± 265.5
Metoclopramide stimulation	Contractions per minute	Sham	4	2.2 ± 1.3	7.4 ± 2.8	8.2 ± 3.2
		Myotomy	5	2.5 ± 2.5	6.6 ± 5.5	5.8 ± 4.2
	Contraction amplitude (mm Hg)	Sham	4	12.1 ± 3.3	65.1 ± 56.0	31.0 ± 22.5
		Myotomy	5	21.4 ± 16.2	51.9 ± 41.6	29.4 ± 25.5
	Cumulative pressure (mm Hg/s)	Sham	4	131.8 ± 48.9	124.1 ± 1,109.8	668.6 ± 549.6
		Myotomy	5	244.8 ± 218.4	985.7 ± 863.3	635.8 ± 580.1

was connected to a transducer coupler (type A; strain gauge bridge) that fed the electrical signals to an analog to digital converter (Coulbourn Instruments). Data were collected and analyzed on an XT 286 microcomputer with a custom-designed software program from National Instruments, Inc. The sinusoidal pressure waves from each transducer were displayed graphically and the program then obtained averages for contraction amplitude (millimeters of mercury), contraction frequency (waves per minute), and cumulative pressure for the 5-minute test (millimeters of mercury per second).

We performed baseline manometry immediately following graft revasculation at the time of operation and again 2 to 3 weeks postoperatively with the animal under light sedation (postrecovery and preintervention [PRPI]). All manometry tests were 5 minutes long and were performed on animals fasted for 24 hours. After each initial test, we repeated manometry at 5 minutes, 1 minute after a temporary motility stimulus (10 mg metoclopramide hydrochloride given intravenously). With baseline data collected and stored, the animals were randomly divided into a sham group (n = 4) and a myotomy group (n = 5). Under an anesthetic regimen similar to that in the tissue transfer operation, the myotomy-assigned animals underwent an S-shaped incision through the neck skin overlying the graft. Dissection continued down to the level of the jejunum, and a longitudinal incision was made through the serosa and both layers of muscle. To ensure complete circumferential discontinuity, the submucosal surface was carefully laid bare of muscle tissue for a width of 0.5 to 1.0 cm along the entire length of the graft (Fig 1C). Occasional rents in the mucosa were repaired with interrupted 4-0 chromic suture. In the sham operation, the approach and dissection went through the subcutaneous tissue to expose the graft, but did not penetrate the serosa or muscle. The wounds were then closed in a layered fashion. All animals received 300 mg ampicillin sodium administered intramuscularly twice a day for 4 days postoperatively.

After complete healing and recovery (2 to 3 weeks from their second operations), both sham and myotomy groups underwent manometric testing with and without metoclopramide (postintervention [PI]).

At the end of the study, all animals were painlessly killed and the grafts were immediately harvested and placed in 10% formalin. Gross and microscopic histology were performed by the Department of Pathology, Jewish Hospital of St Louis. All data collected were analyzed by a statistician using the Wilcoxon nonparametric test.

RESULTS

All nine animals survived the initial operation and had primarily viable free jejunal grafts. The average ischemia time was 2 hours. The graft length averaged 19 cm in the sham group and 20 cm in the myotomy group (range 15 to 25 cm). The wounds healed well after both primary free tissue transfer and surgical interventions. However, three of the five myotomy dogs developed temporary fistulae, probably due to occult microperforations caused by surgical trauma.

Figure 2A shows a representative tracing of waveforms from the three transducer probes in a graft during PRPI baseline testing. Figure 2B shows contractile activity in the same graft after injection of metoclopramide. Results from the motility studies are shown in the Table. Because the group sizes were small, statistical analysis of the data was nonparametric. All data had large standard deviations, and therefore statistical differences ($p < .05$, Wilcoxon test)

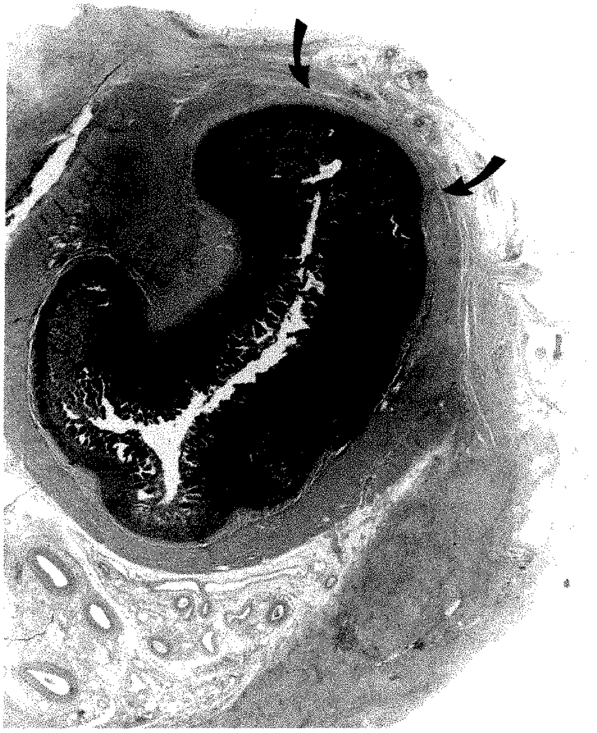

Fig 3. Postmyotomy histology showing cut end of circular and longitudinal muscle layers with ingrowth of fibrous scar tissue between arrows.

within and between groups were difficult to establish.

Each manometric test was first performed with the graft in the resting or baseline state. We anticipated that there would be low-grade contractile activity at this baseline. With this low activity possibly being reduced even further by myotomy, difficulty in detecting small differences in motility within and between grafts was predicted. Therefore, each graft was retested after injection of metoclopramide (Reglan, AH Robins), a potent stimulator of gut activity, to determine the potential maximum activity of the graft. The longitudinal jejunal myotomy was an effort to completely abolish not only baseline contractile activity, but also the potential for high-grade contractions seen at certain phases of the digestive cycle. The random assignment of dogs to the two intervention groups resulted in the following. The sham group, when tested at baseline before intervention, demonstrated a significantly decreased ($p < .02$) mean cumulative pressure (millimeters of mercury per second) for the 5-minute test versus the group randomized to myotomy. However, the group means were similar under a metoclopramide stimulus (see Table). We are unable to explain this peculiarity, but believe it may reflect our small group sizes. We did observe large individual differences in spontaneous graft contractility; thus, chance assignment of grafts with low activity to the sham group may have occurred.

There was a trend toward an increase in graft contractile activity from the time of operation to PRPI for the myotomy group, at baseline, and for both groups with metoclopramide. In no case, however, was this change statistically significant. The sham group activity was decreased, but not significantly (see Table).

Although there was a trend to decreased graft activity after myotomy, with a mean decrease in all parameters both with and without metoclopramide, there was not a statistically significant decrease within the group, ie, PRPI versus PI. Mean total graft work decreased 20% at baseline after myotomy and 36% in the metoclopramide-stimulated mode. The sham surgery dogs did 380% more baseline work after intervention, but 44% less metoclopramide-stimulated work. There was also no significant difference in activity between the sham surgery group and the myotomy group after intervention, either at baseline or with metoclopramide. In short, the longitudinal myotomy did not demonstrate the ability to significantly diminish contractile activity as measured by solid-state manometry.

DISCUSSION

Ever since the pioneering work[11] of Mikulicz, Gluck, Trotter, Wookey, and others, surgeons have searched for the ideal reconstruction following total laryngopharyngectomy and/or cervical esophagectomy. The primary goal is to establish orogastric transit sufficient for the patients' nutritional needs.

One-stage repair using the free jejunal autotransplant with microvascular anastomosis is successful and popular, but may leave the patient with functional dysphagia. This can be caused by attempting to swallow against a circumferentially contracted graft. Such contraction could also potentially inhibit tracheoesophageal or tracheojejunal phonation. We have noted starts and stops in speech continuity in these patients, possibly due to graft contraction.[12]

The present study reports the results of delayed surgical myotomy performed on microvascular free jejunal grafts in dogs. The original model[9] has been modified to facilitate long-term study of the jejunal segment.

We observed a wide range of spontaneous baseline activity from graft to graft after revascularization. This unpredictable behavior persisted after a sham operation, with baseline pressure parameters (frequency, amplitude, and cumulative pressure) apparently increasing postoperatively. Under conditions of preoperative and postoperative metoclopramide stimulation, however, sham-operated dogs showed a trend to diminished activity. After the myotomy, despite the disrupted grafts' showing reduced activity on all parameters both with and without a metoclopramide stimulus, this trend was not statistically significant. Furthermore, pressure parameters between the myotomy group and the sham group were not significantly different. This suggests that even though the myenteric plexus is surgically interrupted, it relies on longitudinal rather than circumferential continuity for continued function. Furthermore, its residual motile function is capable of generating near-normal intraluminal pressure, despite discontinuity. One additional possibility to explain this would be restoration by scar tissue of a physical connection between the cut muscle margins. We were able to document this phenomenon histologically in sampled grafts (Fig 3). The manometry findings were contrary to our hypothesis that myotomy would cause total or near-total ablation of contractility. The rather small magnitude of reduction in average pressure parameters in myotomized grafts and the equivalence of sham surgery to myotomy surgery is strong experimental evidence that the myotomy we performed was ineffective. The next phase of this experimentation will study the effects of other forms of intervention, including drugs and radiotherapy.

CONCLUSIONS

1. A 3-month study of exteriorized jejunal free flaps is feasible in dogs, avoiding gross intussusception (Fig 1D).
2. Immediate postoperative motility is not predictive of activity in the healed, postoperative state.
3. Delayed myotomy of jejunal free flaps is feasible despite some temporary complications.
4. A trend to decreased motility in myotomized grafts is not clinically or statistically significant.
5. There is no significant difference in motility between myotomized grafts and sham-operated grafts.
6. Future research to modify jejunal graft motility should include other modalities, eg, pharmaceutical or radiotherapeutic.

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FUNCTIONAL NECK DISSECTION: THREE DECADES OF CONTROVERSY

JAVIER GAVILÁN, MD
MADRID, SPAIN

CÉSAR GAVILÁN, MD
MADRID, SPAIN

JESÚS HERRANZ, MD
LA CORUÑA, SPAIN

Functional neck dissection (FND) is a neck-functional, tumor-radical approach for the management of the neck in patients with head and neck cancer. Based on the anatomic knowledge of the lymphatic compartments of the neck, FND is a different surgical technique rather than a modification of the classic procedure described by Crile. From an oncologic viewpoint, FND is a relatively safe operation to treat the cervical spread from head and neck cancer as long as the indications and technical details are carefully followed. In this report, based on our experience with more than 1,000 FNDs, we analyze the history and the philosophy of the operation.

KEY WORDS — functional neck dissection, head and neck cancer.

The proper management of the neck in patients with head and neck cancer is one of the unresolved oncologic questions. Cervical metastases are the only certain risk factor and the best prognostic indicator for patients with head and neck cancer.

Since 1906 the so-called radical neck dissection has been the principal tool in the management of cervical metastases in patients with head and neck cancer.[1] The operation, described by Crile, completely removes the lymphatic system of the neck along with a number of functional and cosmetically important structures. To avoid the unnecessary removal of these structures, several conservation procedures have been used since the 1920s. One of them is the functional neck dissection (FND), which has been the subject of controversy for the last 30 years.

The anatomic basis for this procedure was developed by Osvaldo Suárez. In 1969 he taught the principles to the senior author (C.G.). Since then, more than 1,000 standardized FNDs have been performed at our institutions. In this report we want to pay recognition to the man who made possible the development of this new therapeutic approach to the neck, which combines oncologic radicalness with surgical conservatism. No statistics on long-term results will be mentioned, since our results with FND have been previously reported.[2]

HISTORICAL DEVELOPMENT

In 1968 one of us (C.G.) was invited to give a course at the University of Córdoba, Argentina, and he met Dr Osvaldo Suárez. At that time Suárez was assigned to the otolaryngology–head and neck surgery department, and also taught in Professor Pedro Ara's department of anatomy. Ara, born in Spain, was a well-known anatomist who became popular as the "Spanish Anatomist" after embalming the cadaver of Eva Perón. The close relationship between Suárez and anatomy is emphasized here because it is key to the understanding of the surgical technique of FND.

The impression of the new surgical technique performed by Suárez was so profound that Suárez was asked to reciprocate our visit by coming to Madrid the next year. In June 1969 Suárez came to our institution and gave a course on neck surgery. For 2 weeks he operated with us daily and taught us the FND. Surgeons from all over Europe attended the course.

Although Suárez did not write extensively about the fundamentals and surgical technique of FND, he must be credited as the first to define the anatomic basis and surgical criteria for FND. His studies confirmed and expanded upon the anatomic concepts described by Truffert in 1922.[3] This led to a revision of the classic principles of neck dissection. Other surgeons have been responsible for the worldwide acceptance of FND, because Suárez only published a few papers regarding the problem of cervical metastases, and none of them in English.[4,5] The FND is almost always mentioned as Bocca's procedure, because Bocca and his group popularized the technique in the English-language literature.[6-9] Calearo, a member of Bocca's group who attended our first course on FND in 1969, with Teatini[9] reported in the English-language literature the surgical technique of FND in a step-by-step manner, as we had in the Spanish-language literature 11 years before.[10]

CONCEPTUAL BASIS

Under normal conditions the whole lymphatic system of the neck lies within a system of fascial

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From the Department of Otorhinolaryngology, La Paz Hospital, Autonomous University, Madrid (J. Gavilán, C. Gavilán), and Juan Canalejo Hospital, La Coruña (Herranz), Spain.

compartments.[4] Lymph nodes and ducts are in close proximity to the muscular, neural, vascular, and glandular structures of the neck, but a fascial barrier separates these structures from the lymphatic system of the neck. In N0 and N1 patients the celluloadipose tissue containing the lymphatic system of the neck can be completely removed by carefully stripping the fascial cover from the muscles, vessels, nerves, and glands. A number of reports have demonstrated that for N0 and N1 disease FND is as effective as the classic procedure.[2,8,11,12] When tumor cells spread beyond the confines of the lymph node capsule — N2 and N3 patients — invasion of the fascial barrier recommends the removal of these structures. In these cases the radical operation is indicated.

Philosophy. Now that FND is widely accepted as a relatively oncologically safe procedure, the problem still remains regarding its philosophy. Most head and neck surgeons consider FND a "modification" of the procedure described by Crile. However, FND is more than a simple "modified neck dissection," because its anatomic and surgical principles are not derived from those of the Crile operation. To be considered a new, different procedure, a surgical technique must be based on new anatomic, physiologic, or pathologic facts, and it must offer some advantages over the alternate operation.[13] The FND is based in solid anatomic concepts derived from fascial compartmentalization of the neck. The idea of fascial spaces of the neck, developed by Suárez,[4] holds the clue to the difference between the procedures.

Nomenclature. During the last three decades, FND has received several names. Suárez called the procedure FND, and we find no reason to change this name. The reason for the multiple names for FND must be sought in the frequent misunderstanding of the real meaning of the word functional when applied to a neck dissection. The term functional has usually been misunderstood as meaning "not aggressive against cancer," when it really means "retaining maximum patient function while not jeopardizing outcome." As stated by Suárez in 1962, "The extent of a radical approach should be conceived against cancer and not against the neck."[5]

Common nomenclature is needed both to facilitate the communication between different institutions and for training programs. For this purpose exhaustive classifications[14] are impractical. Young surgeons in training need a practical classification in order to learn the fundamentals of neck surgery. After learning the basic principles of neck surgery they will be able to widen their surgical techniques to fit the operation to the problem on a more individualized basis.

Time and Difficulty. It is frequently mentioned in the literature that FND is a technically difficult and time-consuming operation that must be performed only by the experienced head and neck surgeon. It has been said that inexperienced surgeons or those performing only a limited number of major procedures in the head and neck should limit their activity to the easier classic operation.[15]

In our opinion, technical difficulty must be combated with the creation of enough well-trained surgeons capable of performing this operation. To recommend more aggressive solutions than those required only because of technical difficulty is nonsense and contributes to stopping the natural evolutionary process of medicine. To quote Sir Charles Ballance, "That the execution of an operation is difficult is no reason why it should be shirked or scamped."[16]

Accepting FND as a more time-consuming procedure than the classic operation for the majority of neck surgeons, the extra time added when performing an FND — 30 to 60 minutes — must be properly evaluated. One hour is not a high price to pay for the lifetime preservation of important anatomic, physiologic, and cosmetic structures, provided oncologic safety is guaranteed.

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THE UCSF OTOLARYNGOLOGY UPDATE: 1992

The UCSF Otolaryngology Update: 1992, will be held November 5-7, 1992, at the Ritz-Carlton Hotel in San Francisco, California. For more information, contact the University of California, Extended Programs in Medical Education, Room LS-105, San Francisco, CA 94143-0742; telephone: (415) 476-4251.

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INTERNATIONAL HEARING AID CONFERENCE
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An International Hearing Aid Conference will be held June 15-17, 1993, at The University of Iowa, Iowa City. For information on registration and accommodation, contact the Conference Center, University of Iowa, Memorial Union, Iowa City, IA 52242; (319) 335-3231, Fax (319) 335-3407. For information on Call for Papers, contact Regina Tisor (319) 356-2471, Fax (319) 356-4547. We have applied for Continuing Education Units from ASHA and HAIC.

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FACTORS PREDICTING POSTOPERATIVE SENTENCE SCORES IN POSTLINGUISTICALLY DEAF ADULT COCHLEAR IMPLANT PATIENTS

PETER J. BLAMEY, PHD
BRIAN C. PYMAN, DLO, FRACS
GRAEME M. CLARK, PHD, FRACS
RICHARD C. DOWELL, MSC, DIPAUD
MICHAEL GORDON, MB,BS
ALISON M. BROWN, BSC, DIPAUD
RODNEY D. HOLLOW, BSC, DIPAUD
EAST MELBOURNE, AUSTRALIA

A sample of 64 postlinguistically profoundly to totally deaf adult cochlear implant patients were tested without lipreading by means of the Central Institute for the Deaf (CID) sentence test 3 months postoperatively. Preoperative promontory stimulation results (thresholds, gap detection, and frequency discrimination), age, duration of profound deafness, cause of deafness, lipreading ability, postoperative intracochlear thresholds and dynamic ranges for electrical stimulation, depth of insertion of the electrode array into the scala tympani, and number of electrodes in use were considered as possible factors that might be related to the postoperative sentence scores. A multiple regression analysis with stepwise inclusion of independent variables indicated that good gap detection and frequency discrimination during preoperative promontory testing, larger numbers of electrodes in use, and greater dynamic ranges for intracochlear electrical stimulation were associated with better CID scores. The CID scores tended to decrease with longer periods of profound deafness.

KEY WORDS — cochlear implantation, profound deafness, promontory stimulation, sentence test.

INTRODUCTION

Since 1982, over 120 patients have been implanted in Melbourne with the 22-electrode cochlear implant manufactured by Cochlear Proprietary Limited.[1] The benefit of the implant to these patients has varied over a considerable range, to the extent that over one third of them have been able to use the telephone for simple conversations[2] and a few have received so little benefit that they do not use the device for more than 1 or 2 hours per week. In the selection and preoperative counseling of the patients, it would be very helpful to be able to predict whether the result was likely to be good or poor. This paper considers a number of factors that might be used to make such a prediction, in the light of the Melbourne experience so far.

A number of previous authors have discussed the possibility that electrical stimulation of the promontory might be used as a preoperative measure of nerve survival and/or likely benefit from a cochlear implant.[3-10] Controversy exists as to the prognostic value of promontory stimulation results, as it has been shown that this procedure may not give a good indication of the percentage of surviving dendrites.[3,5] Cases of poor or negative promontory stimulation responses associated with good implant outcome have been reported.[4,6] However, some correlation has been found between preoperative and postoperative data in some patient populations.[7,8,10] In assessing the usefulness of promontory stimulation data it is also relevant to consider the correlation (if any) of preoperative thresholds with postoperative intracochlear thresholds. If these two measures are both related to the size of surviving neural populations, one would expect them to be highly correlated with one another. The present analysis includes intracochlear as well as promontory thresholds.

Previous studies[11-14] have shown correlations of patient age and duration of deafness with postoperative speech results. Other variables included in this analysis were cause of deafness, which is known to affect the survival of ganglion cells in profound deafness,[15] and depth of insertion of the electrode array into the scala tympani, which is known to affect the range of pitch sensations produced.[16] A variable that is similar to the depth of insertion is the number of electrodes in use in the patient's speech processor. This number is particularly important in the coding strategy of the Cochlear prosthesis, because it affects the number of frequency steps that are available to code the spectral peaks. Number of electrodes in use and dynamic range of electrical stimulation have both been found to be related to vowel and consonant recognition in patients using the Cochlear prosthesis.[11,12]

METHODS

From the patients implanted in Melbourne, a sample of 64 postlinguistically deaf adults and teenagers whose native language was English was chosen. Children still developing spoken language, prelinguistically deaf adults and teenagers with poorly developed spoken language, and foreign language speakers were excluded because of the overriding

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From the Department of Otolaryngology, University of Melbourne, East Melbourne, Australia.

REPRINTS — Peter J. Blamey, PhD, Dept of Otolaryngology, University of Melbourne, 32 Gisborne St, East Melbourne, Victoria 3002, Australia.

factor of language competence that applies to these groups.

Preoperatively, all of these patients underwent transtympanic promontory stimulation. An uninsulated fine-gauge needle was passed through the posterior-inferior quadrant of the tympanic membrane approximately halfway between the umbo and the annulus onto the promontory. In some cases topical anesthesia was used. The electrode was held in place by an aural speculum with a small magnet on its inner wall. The ground electrode was placed on the ipsilateral cheek.

Over the years in which the data were collected, the current waveform used for promontory stimulation was changed from biphasic pulses of short duration to a square wave with a 100% duty cycle. The change was made because it was found that the threshold of pain was lower relative to the threshold for sound sensations with the pulsatile waveform. The first 14 patients were tested with the pulsatile waveform, and the rest were tested with square waves. In order to compensate for the different waveforms, the pulsatile thresholds were converted to equivalent square wave currents with the same charge per phase.

Each patient was implanted with the 22-electrode intracochlear implant developed by the University of Melbourne and Cochlear Proprietary Limited.[1,17] Intracochlear thresholds and maximum comfortable levels were measured by the audiologist, and the wearable speech processor was programmed. For the first 10 weeks after the operation, the patients were counseled in the use of the implant and given practice at various communication tasks. The threshold and comfortable levels were adjusted as the patients became more familiar with the sounds. At the end of the 10 weeks, the patients were evaluated with a number of speech tests, including the Central Institute for the Deaf (CID) Everyday Sentence Test.[18] This test consists of lists of 10 everyday sentences containing 50 key words. The patient's score is the number of key words recognized. The test was presented from a tape recorder, in a free field at a level of 65 to 70 dB sound pressure level by means of the wearable speech processor and the ear-level microphone, and without lipreading. This test was selected for use in this study because the result was available for most patients and, of all the tests, it most closely estimates the benefit of implantation to the patient in real conversational situations.

During the period in which the data were collected, the wearable speech processor was improved. The largest change occurred with the introduction of a two-formant (F0F1F2) speech coding scheme to replace the original single-formant (F0F2) scheme.[11,19,20] To compensate for the effect of this change, the CID sentence scores of the 16 patients who used the F0F2 processor were multiplied by a constant factor (2.15), making the mean score for this group equal to the mean score of the remaining 48 patients who used the F0F1F2 processor. This procedure removes the effect of the processor change from the statistical analyses that follow.

One further adjustment to the data was required before the statistical analysis. It is possible to program the 22-electrode implant in several different electrode configurations, known as common ground, bipolar, bipolar-plus-one, bipolar-plus-two, etc. In the common ground mode, the electrical current flows between a selected electrode and all other electrodes of the array. In the bipolar modes, current flows between two selected electrodes. The selected electrodes are adjacent in the bipolar mode, have one unselected electrode between them in the bipolar-plus-one mode, and so on. Each mode produces a different intracochlear threshold, because the electrical current distribution in the cochlea is different. Forty-two patients used the bipolar-plus-one mode, and the intracochlear thresholds for the other patients were corrected to equivalent bipolar-plus-one values. The corrections were made by adding the average differences between threshold levels for different electrode configurations measured in a separate experiment for three patients (see Appendix).

RESULTS

Table 1 summarizes the distribution of each variable for the group of patients. Not all of the data were available for every patient, especially promontory stimulation thresholds, as these were not always measured at all three pulse rates. No attempt was made to reach a threshold for sound at levels higher than the threshold for pain. Out of the 64 patients, 58 reported hearing a sound for at least one frequency of stimulation. The current level steps used to measure intracochlear thresholds correspond to equal ratio increments of about 2%, with level 200 corresponding to 1.5 mA. The waveform used was a biphasic pulse with duration of 200 μs per phase and various rates between 100 and 200 pulses per second. The threshold values used in the analysis were those programmed into the speech processor at the time the CID sentence test was carried out.

In addition to the variables listed in Table 1, each patient was assigned a "stim-code" that summarized the frequency discrimination and gap detection performance during promontory stimulation. A stim-code of 1 was assigned to 29 patients who showed no evidence of discrimination of the different pulse rates used, and poor gap detection thresholds (greater than 50 milliseconds). Twenty-four patients who showed evidence of frequency discrimination or good gap detection but not both were assigned a stim-code of 2. Eleven patients who showed both

TABLE 1. SUMMARY OF VARIABLE DISTRIBUTIONS FOR PATIENT SAMPLE

Variable	*N*	*Minimum*	*Maximum*	*Mean*	*SD*
Age (y)	64	14	75	50.0	15.8
Duration (y)	64	1	53	14.6	12.5
Hearing (dB HTL)	61	90	125*	115.2	10.5
T-50 (μA)	39	1	128	16.0	20.5
S-50 (μA)	29	1	128	18.3	23.4
T-100 (μA)	56	1	188	21.4	26.7
S-100 (μA)	41	1	188	21.4	29.3
T-200 (μA)	41	1	113	32.4	30.8
S-200 (μA)	25	1	90	23.8	24.6
T-basal (cl)	61	60	230	115.3	29.3
T-middle (cl)	61	57	197	117.4	29.7
T-apical (cl)	59	15	221	109.0	39.0
Range (cl)	59	8	108	42.5	21.0
Electrodes	59	9	21	17.3	3.6
Depth (mm)	64	10	25	20.3	3.4
CID (%)	61	0	100	33.2	28.4
CID-lip (%)	38	4	88	47.4	22.2

N — number of patients for whom data were available for each variable; age — patient's age at implantation; duration — length of profound deafness prior to implantation; hearing — minimum hearing threshold for acoustic signals in decibels hearing threshold level (dB HTL) for frequencies 0.5, 1, 2, and 4 kHz measured preoperatively in implanted ear; T-50, T-100, T-200 — promontory stimulation thresholds in microamperes (μA) at which any sensation was first detected for square wave currents at 50, 100, and 200 Hz, respectively; S-50, S-100, S-200 — corresponding thresholds for detection of hearing sensation (ie, excluding tactile, pain, throbbing, and other sensations); T-basal, T-middle, T-apical — thresholds measured in current levels for hearing sensations with intracochlear pulsatile stimulation at most basal, middle, and most apical electrodes used by patient; range — number of current level (cl) steps between threshold and maximum comfortable level on middle electrode; electrodes — number of intracochlear electrodes used to code speech; depth — length of electrode array inserted into scala tympani through round window as estimated by surgeon at time of implantation; CID — postoperative open-set CID Sentence Test score for hearing without lipreading; CID-lip — score on different list from CID Sentence Test presented from videotape as lipreading test with no auditory signal.

*Value 125 dB was used for 27 patients who did not respond to sound at limit of audiometer.

TABLE 2. SIGNIFICANT CORRELATIONS BETWEEN PAIRS OF VARIABLES

Variables	*r*	*p*	*N*
T-50 and S-50	.985	.000	29
T-50 and T-100	.924	.000	37
T-50 and S-100	.964	.000	25
T-50 and T-200	.628	.000	32
S-50 and T-100	.951	.000	27
S-50 and S-100	.966	.000	24
S-50 and T-200	.600	.002	23
T-100 and S-100	.998	.000	41
T-100 and T-200	.767	.000	39
T-100 and S-200	.818	.000	23
S-100 and T-200	.805	.000	28
S-100 and S-200	.820	.000	19
T-200 and S-200	.997	.000	25
T-basal and T-middle	.326	.010	61
T-basal and T-apical	.446	.000	59
T-middle and T-apical	.580	.000	59
T-basal and electrodes	−.431	.001	59
T-apical and electrodes	−.339	.010	57
Electrodes and depth	.278	.033	59
Range and electrodes	.273	.037	59
Duration and age	.391	.001	64
Duration and stim-code	−.344	.005	64
Duration and CID	−.421	.001	61
Age and stim-code	−.334	.007	64
Age and CID	−.319	.012	61
Stim-code and CID	.449	.000	61
T-basal and age	.324	.011	61
T-basal and CID	−.272	.039	58
T-middle and duration	.268	.037	61
Electrodes and CID	.429	.001	56
Range and CID	.398	.002	56

r — Pearson correlation coefficient, p — probability of achieving correlation coefficient of magnitude greater than r by chance, N — number of patients for whom values of both variables were available. Other abbreviations as in Table 1.

were assigned a stim-code of 3. It was not always possible to carry out the full promontory stimulation procedure, so some patients with stim-codes of 1 and 2 might have received a higher stim-code if the procedure had been completed. Patients were also classified according to their cause of deafness: 29 unknown, 10 otosclerosis, 7 meningitis, 6 trauma, and 12 other (including radiation damage, antibiotic ototoxicity, syphilis, autoimmune disease, Meniere's disease, Usher's syndrome, and mumps).

Several statistical analyses were carried out on the data. First, a Pearson correlation coefficient was calculated for each pair of variables. Table 2 shows those correlation coefficients that were significantly different from zero with $p<.05$.

The second analysis consisted of a number of *t* tests comparing the groups of patients with a particular cause of deafness (otosclerosis, meningitis, and trauma) with the rest of the patients as a group. The independent variables included all those listed in Table 1 together with the stim-code. No significant differences were found for the trauma cases. T-50, S-50, T-100, and S-100 (defined in Table 1) were significantly higher for the meningitic patients than for the others; however, this was because one patient had promontory stimulation thresholds that were three to four times higher than those of any other patient tested. This difference may have been due to poor electrode placement, because the intracochlear thresholds for this patient were not particularly high compared to the rest of the sample. As shown in Table 3, the otosclerotic patients were 15 years older on average. There were marginally significant differences in the "electrodes," CID-lip, and CID variables as well. No other variables showed significant differences between the otosclerosis group and the rest of the patients.

The third analysis was an analysis of variance with stim-code as the independent variable and CID sentence score as the dependent variable. The analysis showed a highly significant effect ($F=7.347$, $df=2, 58$, $p<.002$). Post hoc analysis using the least significant difference test indicated that the average CID scores for all three levels of stim-code were significantly different. The average scores were 20.7%, 36.3%, and 55.6% for stim-code values 1, 2, and 3, respectively. This result is consistent with the signif-

TABLE 3. DIFFERENCES BETWEEN PATIENTS HAVING OTOSCLEROSIS AND REST OF PATIENTS

	Otosclerotic Patients		*Other Patients*			
Variable	*Average*	*N*	*Average*	*N*	t	*p*
Age (y)	62.5	10	47.7	54	−2.873	.006
Electrodes	15.6	10	17.7	49	1.706	.093
CID-lip (%)	35.5	8	50.6	30	1.755	.088
CID (%)	19.7	10	35.8	51	1.661	.102

N — number of patients in each group for whom data were available, *t* — Student's *t* statistic used to test whether group means were significantly different, p — probability that value of *t* greater than that shown would be achieved by chance. Other abbreviations as in Table 1.

TABLE 4. COEFFICIENTS FROM MULTIPLE REGRESSION OF CID SENTENCE SCORES

Variable	*Coefficient*	*Standard Error*	t	*p*
Stim-code	10.55	4.36	2.42	.019
Electrodes	2.05	0.89	2.30	.026
Range	0.33	0.15	2.22	.031
Duration	−0.53	0.26	2.04	.046

t — Student's *t* value used to test whether regression coefficient is significantly different from zero, p — probability that *t* value of magnitude greater than that shown would occur by chance. Other abbreviations as in Table 1.

icant correlation shown in Table 2.

The final analysis was a stepwise linear regression with CID score as the dependent variable and age, duration, hearing, T-apical, T-middle, T-basal, range, electrodes, depth, stim-code, CID-lip, and otosclerosis as the independent variables (defined in Table 1). Otosclerosis was included as a two-valued variable that was 1 for patients whose cause of deafness was otosclerosis and zero for all other patients. The promontory stimulation thresholds and the etiology groupings other than otosclerosis were not included because the earlier analyses indicated no significant effect of these variables on CID sentence scores. A stepwise linear regression was carried out to determine which independent variables produced a significant increase in the variance accounted for by the regression function. Four of the variables produced regression coefficients that were significantly different from zero with $p<.05$. These coefficients are summarized in Table 4. The regression produced a highly significant result ($F=9.69$, $df=4, 51$, $p<.0001$) and accounted for 43.2% of the variance in the data.

DISCUSSION

Promontory Stimulation Thresholds. The thresholds for electrical stimulation of the promontory were consistent across frequency. The means and ranges of threshold values in Table 1 were similar for the different pulse rates, and the high correlations in Table 2 indicate that patients with low thresholds at one frequency also had low thresholds at other frequencies. The range of threshold currents was similar to that observed in the study of Rothera et al.[9] Despite the consistent nature of these measures, no correlation was found with postoperative intracochlear thresholds or CID sentence scores. It is thus unlikely that promontory stimulation thresholds could be used as a predictor of cochlear implant outcome. Possible explanations of the low correlation of promontory and intracochlear thresholds include the variable placement of the promontory electrode, and the broad spread of electrical current that would be influenced by anatomic differences and the electrical properties of surrounding structures. Hochmair-Desoyer and Klasek[10] have reported some correlation between thresholds for promontory stimulation and intracochlear stimulation with a different intracochlear electrode array. Their threshold measures were not correlated with the degree of success of implantation as indicated by speech recognition measures, in accord with the present study.

Frequency Discrimination and Gap Detection During Promontory Stimulation. In contrast to the thresholds, the stim-code measure of discrimination of temporal characteristics of waveforms above threshold levels during promontory stimulation did show a consistent relationship with CID scores. It is not known whether the stim-code would be consistent with similar measures using intracochlear stimulation, but it seems likely that this would be the case. At least one previous study[21] has found a similar relationship between speech scores and gap detection thresholds for cochlear implant patients. Given these results, there does seem to be some justification for using electrical stimulation of the promontory as a prognostic procedure before cochlear implantation. It has also been reported anecdotally that patients find it useful to experience the sounds produced by electrical stimulation in forming a realistic expectation of the outcome. In this regard, it has been found very helpful to set up a single-electrode speech processor during promontory stimulation to give the patient a preliminary experience of listening to coded speech.

Postoperative Intracochlear Thresholds. The significant correlations between T-basal, T-middle, and T-apical indicate that there was a tendency for intracochlear thresholds to be similar along the length of the electrode array, ie, a patient with a low threshold in the basal region was also likely to have low thresholds in the middle and apical regions of the array. There were some correlations with other variables in Table 2, such as duration, age, and CID sentence scores. One possible explanation of these trends may be that there is an underlying degeneration of the auditory neurons during deafness that affects both the intracochlear thresholds and the CID sentence scores. The signs of the correlation coefficients indicate that thresholds increase with longer duration of deafness, and CID scores decrease with increasing thresholds. These effects are consistent with the suggested explanation. This link between thresholds and CID scores is a relatively weak one compared to the effects that were found in the regression analysis that is discussed below.

Dynamic Range of Intracochlear Stimulation. It is somewhat surprising that there was no negative correlation between intracochlear thresholds and range, since the range is equal to the difference between the maximum comfortable level and the threshold. (Correlation coefficients for range and T-basal, T-middle, and T-apical were −.026, −.193, and −.183, with p values of .848, .143, and .173, respectively.) This lack of significant correlation suggests that the absolute thresholds are determined mainly by geometric and electrical properties of the cochlea and electrode array, while dynamic ranges may be affected by independent parameters such as neural survival. The dynamic range affects the loudness variations between electrically coded speech sounds. Such loudness variations are important in recognizing many suprasegmental and segmental features of speech. A larger dynamic range may allow a better representation of loudness and thus a better speech recognition score. The Viennese study[10] found a similar correlation between speech recognition results and dynamic range, and no significant correlation between thresholds and dynamic range.

Number of Electrodes in Use. The speech coding scheme used by the F0F1F2 speech processor uses the full extent of the electrode array to encode the first and second formant frequencies. These frequencies are well known to provide information useful in the recognition of vowels and consonants. The amount of frequency information present in the electrical stimulus is increased if a larger number of electrodes is used. The positive correlation between CID scores and number of electrodes indicates that the patients with more electrodes in use can take advantage of this extra information. The minimum number of electrodes in use was 9 and the maximum was 21. The regression analysis indicates that this difference of 12 electrodes may account for a 24% difference in CID score — a difference that would be of marked benefit to the patient.

The significant negative correlations between intracochlear thresholds and number of electrodes may be due to the effect that the geometric and electrical properties of the cochlea have on these variables. One of the most common reasons for a decrease in the number of electrodes is bone growth in the cochlea restricting the insertion of electrodes. A second reason is that uncomfortable sensations are often associated with high thresholds on basal electrodes. In this case, the electrodes producing the uncomfortable sensations would not be used in speech coding.

Depth of Insertion. Depth was correlated with CID at a marginal significance level ($r = .225$, $p = .081$, $N = 61$). This variable may be important in several different ways. First, the overall sharpness or place pitch sensation produced by an electrode depends on its position in the cochlea. Greater depths of insertion lead to lower place pitch sensations and more natural speech sounds produced by the implant.[16] Second, there is some evidence that nerve survival tends to be greater in apical regions of the cochlea than in basal regions, so deeper insertion of the electrode array may improve the perception of speech. Finally, shorter depths of insertion may be related to the shape of the spiral or bony growth within the cochlea, which might affect electrical current distributions during stimulation. These different current distributions may affect the neural excitation patterns produced during speech coding. It is not possible to tell from the present study which of these effects is most important.

Depth was significantly correlated with number of electrodes, so the significance of number of electrodes in the regression analysis may include a contribution due to depth of insertion.

Lipreading Ability. The variable CID-lip was not significantly correlated with any other variable and did not have a significant effect on the regression analysis.

Age and Duration of Deafness. As discussed above, it is possible that an underlying degenerative process accounts for the negative correlations of age and duration with CID sentence scores and intracochlear thresholds. A strong negative correlation between duration of deafness and spiral ganglion cell count has also been found by Nadol et al.[15]

Cause of Deafness. Although the cause of deafness has been found to affect the number and distribution of surviving auditory neurons,[15,22] the only group that was different from the rest of the patients was the otosclerosis group. In the study of Nadol et al,[15] otosclerosis as opposed to other causes was found to have a relatively small effect on spiral ganglion cell survival. It may be that the importance of otosclerosis is related to the electrical properties of the bone in the region of the cochlea, affecting the current distributions produced by the electrodes, rather than a direct effect on the neural responses. Another possibility is that the marginally lower CID scores arose from the higher average age of the otosclerotic patients.

Preoperative Hearing Thresholds. All of the patients were very deaf, so the variations in residual hearing among the group were not great. Only one patient had a three-frequency (at 0.5, 1, and 2 kHz) average threshold less than 110 dB hearing threshold level, and 27 patients had no measurable hearing at any frequency. The preoperative residual hearing level in the implanted ear was not correlated significantly with any other variable and did not contribute significantly to the regression analysis.

Regression Analysis. The regression analysis indicates that there are some factors that can be used to indicate likely postoperative performance of postlinguistically deaf implant candidates on CID sentences. The regression equation is

$$\begin{aligned}\mathrm{CID} = {} & 10.55(\text{stim-code}) + 2.05(\text{electrodes}) \\ & + 0.33(\text{range}) - 0.53(\text{duration}) - 26.92\end{aligned}$$

This equation predicts a CID sentence score of 62% for "ideal" candidates who demonstrated good frequency discrimination and gap detection performance during promontory stimulation, used the full set of 20 bipolar-plus-one electrode pairs, had a good dynamic range of 50 current levels, and were deafened very recently. In contrast, the equation predicts a score of −7% (ie, close to zero) for "poor" candidates who could not discriminate frequencies or detect short gaps during promontory stimulation, used only 10 electrodes, had a dynamic range of 15 current levels, and were deafened 20 years before implantation. The regression analysis predicts average scores rather than a score for an individual, and it must be remembered that considerable variability was not accounted for by the regression. These predictions should therefore be treated cautiously and not be used as a guarantee of success for the patient. In particular they should not be applied to prelinguistically deafened candidates or to young children, who were excluded from the sample in this study.

The data are also dependent on the speech processor and implant system used and are not easily generalized to other cochlear implant systems, although similar trends might be expected. Improvements in speech processing strategies in the near future[23] are likely to improve average CID sentence scores to levels above those predicted by the regression equation. It should also be remembered that the CID sentence data were collected approximately 3 months after the operation, and patient performance continues to improve for several years postoperatively.[24]

Two of the variables in the regression (electrodes and range) are not available preoperatively, although it may be possible to estimate the number of electrodes that can be inserted into the scala tympani from good-quality radiography.

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APPENDIX

APPROXIMATE ADJUSTMENT OF INTRACOCHLEAR THRESHOLD VALUES FOR DIFFERENT ELECTRODE CONFIGURATIONS

At the reviewers' request, the data used for this adjustment are included here. The different electrode configurations or modes of stimulation with the 22-electrode Cochlear prosthesis produce different electrical current distributions in the cochlea. Thus, the threshold current levels will be different for different modes. If it is assumed that threshold corresponds to stimulation of a small number of auditory nerve fibers close to the maximum of the current distribution, the ratios of the threshold currents for different modes will depend on geometric factors only and will be approximately the same for different patients. In considering the common ground mode of stimulation, the geometric factors are different for different active electrodes, depending on their distances from the ends of the array. Thus, different current ratios will apply to the basal, middle, and apical electrodes.

Estimates of the adjustments were made by measuring the hearing thresholds with different modes of stimulation for three patients (see Table below). The mean adjustments from the table were −24 levels for bipolar, +12 levels for bipolar-plus-two, and +18 levels for bipolar-plus-three. To adjust common ground thresholds, the adjustments were +26 levels for basal, −7 levels for middle, and −2 levels for apical electrodes. The adjustment was added to the measured thresholds to calculate the approximate equivalent threshold in bipolar-plus-one mode. Note that a fixed difference on the current level scale corresponds to a fixed ratio of actual current values. In the group reported, eight patients used common ground, four used bipolar, six used bipolar-plus-two, and one used bipolar-plus-three stimulation.

The assumption above is a crude one and is not valid for comfortable levels. It is *not recommended* that this adjustment be used in setting patient stimulation levels in different modes.

THRESHOLD CURRENT LEVEL DIFFERENCES RELATIVE TO BIPOLAR-PLUS-ONE STIMULATION FOR THREE PATIENTS

	Basal Electrode			*Middle Electrode*			*Apical Electrode*		
Mode	*Pt 16*	*Pt 36*	*Pt 67*	*Pt 16*	*Pt 36*	*Pt 67*	*Pt 16*	*Pt 36*	*Pt 67*
Common ground	−34	−18	—	11	11	−2	−5	14	−4
Bipolar	24	32	—	30	—	—	26	7	—
Bipolar-plus-two	−5	−22	—	−7	−5	−42	−12	−4	−10
Bipolar-plus-three	−17	−37	—	−26	−5	—	−16	−10	−11

Patient numbers refer to list of all patients implanted in Melbourne, and have been used in previous publications. Normal stimulation modes were bipolar-plus-one for patients 16 and 36, and common ground for patient 67. Basal electrodes produced unpleasant sensation for patient 67, and no hearing threshold was measurable in bipolar-plus-one mode. Hearing thresholds were not reached in bipolar mode for middle electrodes of patients 36 and 67 or apical electrode of patient 67, even at highest level of stimulation.

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ANGIOGENIC GROWTH FACTORS: THEIR EFFECTS AND POTENTIAL IN SOFT TISSUE WOUND HEALING

DAVID B. HOM, MD ROBERT H. MAISEL, MD

MINNEAPOLIS, MINNESOTA

Since their discovery 30 years ago, angiogenic growth factors have been demonstrated to stimulate neovascularization in vitro and in animal studies. Over the last decade, knowledge gained in the field of angiogenic growth factors has grown immensely. These angiogenic growth factors exist in four major families: fibroblast growth factor (FGF), transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF). Each has the ability to induce soft tissue vascularization in microgram quantities. In animal models, FGF, TGF-β, PDGF, and EGF have been shown to enhance soft tissue wound healing. In human clinical trials, EGF and a mixture of PDGFs have been demonstrated to accelerate epidermal regeneration in cutaneous wounds. These factors have considerable therapeutic potential in the areas of soft tissue wound healing and otolaryngology. This article reviews important aspects of angiogenic growth factors and discusses their future potential in soft tissue wound healing.

KEY WORDS — blood vessels, growth substances, wound healing.

INTRODUCTION

Angiogenic growth factors are recently discovered proteins that have the ability to induce vascularization. In microgram quantities, they can induce vascular proliferation in soft tissue. There are four major families of angiogenic growth factors (Table 1): fibroblast growth factor (FGF), transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF). All members of these families induce vascularization in vivo, thus establishing them as angiogenic substances.

Originally, growth factors were named after the target cell or source that led to their discovery. Today, however, the given name can be misleading because it may not fully describe the activities of the factor in question. For example, FGF was initially named for its ability to stimulate fibroblast replication and mobility; but since its discovery, it has been found to be a potent angiogenic protein. Thus, each growth factor can have a multitude of actions on various target cells.

Most polypeptide growth factors are able to stimulate angiogenesis. Because of their ability to induce vascularization, angiogenic growth factors offer a promising potential in soft tissue wound healing. Table 2, adapted from King et al,[1] summarizes some of the known effects of these factors on cells involved in soft tissue wound healing.

NATURE OF ANGIOGENIC GROWTH FACTORS

Angiogenic growth factors are believed to stimulate vascular endothelial cells by either direct or indirect action (see Figure). The direct-acting growth factors specifically stimulate migration and mitosis of vascular endothelial cells by binding to specific membrane surface receptors on endothelial cells.[2] Once the growth factor has bound to the endothelial cell surface receptor, an unknown cascade of intracellular events occurs that results in cellular replication and/or chemotaxis. The indirect-acting growth factors have no direct stimulatory effect on vascular endothelial cells in vitro, but induce angiogenesis by an indirect means in vivo. This mechanism is thought to be mediated by macrophages, which in turn secrete a direct-acting growth factor.[3]

The action of growth factors can be complex. Depending on the presence of other peptides, a growth factor may display either stimulatory or inhibitory activities within the same cell. For example, in vitro, TGF-β stimulates the growth of certain fibroblasts in the presence of PDGF, but inhibits their growth in the presence of EGF. Also, one growth

TABLE 1. ANGIOGENIC GROWTH FACTORS

Families	*Members*
Fibroblast growth factor (FGF)	Acidic FGF Basic FGF
Transforming growth factor beta (TGF-β)	TGF-β 1 TGF-β 2 TGF-β 3 Bone morphogenic proteins
Epidermal growth factor (EGF)	EGF TGF-α
Platelet-derived growth factor (PDGF)	PDGF AA PDGF AB PDGF BB

From the Division of Facial Plastic and Reconstructive Surgery, Department of Otolaryngology–Head and Neck Surgery, University of Minnesota Hospital, and Hennepin County Medical Center, Minneapolis, Minnesota.

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REPRINTS — David B. Hom, MD, Division of Facial Plastic and Reconstructive Surgery, Dept of Otolaryngology–Head and Neck Surgery, Box 396, University of Minnesota Hospital and Clinic, Harvard St at East River Rd, Minneapolis, MN 55455.

TABLE 2. ANGIOGENIC GROWTH FACTORS AND THEIR EFFECTS IN SOFT TISSUE HEALING

Growth Factor	*Sources*	*Target Cells*	*Effect*
FGF	Macrophages, endothelial cells	Endothelial	Chemotaxis or replication
		Fibroblast	Chemotaxis or replication, collagenase production
TGF-β	Macrophages, platelets	Endothelial	Stimulates or inhibits replication
		Fibroblast	Chemotaxis, collagen synthesis, collagenase production, stimulates or inhibits replication
EGF	Macrophages, platelets, epithelium	Endothelial	Chemotaxis or replication
		Fibroblast	Chemotaxis or replication, collagenase production, epithelial chemotaxis or replication
		Epithelial	Chemotaxis or replication
PDGF	Platelets, endothelial cells, macrophages	Endothelial	Probable angiogenic role
		Fibroblast	Chemotaxis or replication, collagen synthesis, collagenase production

Adapted from King et al.[1] Descriptions in this Table are examples, and not totally exclusive.

FGF — fibroblast growth factor, TGF-β — transforming growth factor beta, EGF — epidermal growth factor, PDGF — platelet-derived growth factor.

factor can alter the binding affinity of another growth factor receptor. For example, PDGF can decrease the affinity of the FGF receptor for basic FGF. Thus, specific growth factors are not necessarily limited to a single physiologic action, but may instead comprise the characters of a complex cellular signal equivalent to a code.[4]

Over the last decade, extensive progress has been made in defining angiogenic growth factors in several areas: identifying and isolating the polypeptides, analyzing their protein structure, sequencing their genes, and characterizing their receptors on cell membranes. Although the in vitro effects of angiogenic growth factors are well explored, considerably less is known about the actions of these factors in vivo because of the difficulty of quantitating the repair process in vivo and the inability to control the concentration of the growth factors at the experimental sites. For example, in assessing the healing of linear incisions, it is difficult to distinguish new tissue from preexisting tissue. Currently, intense investigations are being conducted by many academic and commercial research centers to explore the effects of angiogenic growth factors in soft tissue wound healing.

FIBROBLAST GROWTH FACTOR

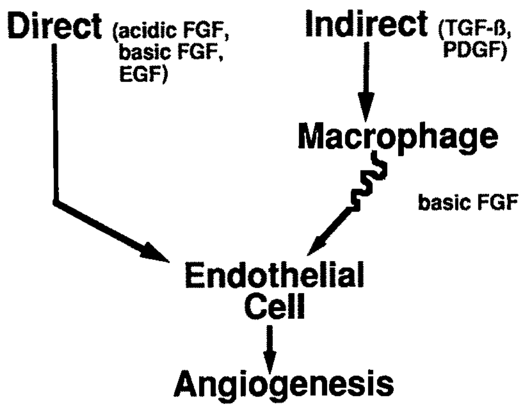
Fibroblast growth factor exists in two closely related forms: basic FGF and acidic FGF. Because of their widespread distribution and wide range of actions, both basic and acidic FGFs have many synonyms (cartilage-derived growth factor, retina-derived growth factor, heparin-binding growth factor, or endothelial cell growth factor). Basic FGF is a protein with a molecular weight of approximately 15,000. It is found in brain, pituitary, retina, corpus luteum, kidney, placenta, adrenals, macrophages, and prostate. Acidic FGF is a polypeptide with a molecular weight of 15,900, and is found in brain and retina.[5]

Both basic and acidic FGFs bind to similar cell surface membrane receptors in a dose-dependent, saturable fashion. Both have identical biologic effects, but in the absence of heparin, acidic FGF is 30 to 100 times less potent than basic FGF. Heparin is believed to increase the potency of acidic FGF by increasing its ability to bind to its receptor and protect it from acid deactivation. In the presence of heparin, acidic and basic FGFs are equally potent and capable of stimulating endothelial cell proliferation and mobilization in vitro at quantities of 1 to 10 ng.[6]

Fibroblast growth factor can also induce replication in many mesenchymal cells, including fibroblasts, chondrocytes, smooth muscle cells, osteoblasts, neural ectodermal cells, and skeletal myoblasts. In most cases, these cells are not only stimulated to proliferate, but also show enhanced differentiation in cell culture.[3] Even though FGF is found in almost all normal tissue, endothelial cell proliferation at these sites is very low.[3] Presently, it is unknown how these potent angiogenic growth factors are controlled in the functionally inactive state.

Studies in Animal Models. Fibroblast growth factor is a potent stimulator of angiogenesis in vivo. In nanogram amounts, the administration of exogenous basic FGF induced rapid neovascularization in the rabbit cornea and on the chick yolk sac.[7] When basic FGF was placed into subcutaneous sponges in rats, a highly vascularized granulation tissue formed within the sponge.[8] By injection of basic FGF into wound incisions in rats, tensile strength increased, even when injections were made 3 days after wounding.[6]

Flap research indicates that FGF has the potential to increase skin flap viability by accelerating flap revascularization. Endothelial cell growth supplement and endothelial cell growth factor (precursors in the FGF family) were placed in Gelfoam and applied to the underside of vascular-compromised skin flaps in rabbits; results suggested that this use of FGF may expedite the neovascularization process in skin flaps when administered in a sustained-release manner.[9] Fibroblast growth factor has also



Mechanisms of angiogenesis by growth factors.

been tested in animal models of impaired healing. In diabetic-induced rats given streptozocin, basic FGF increased the cellularity of granulation tissue within subcutaneous sponges.[10] Thus, FGF may become promising to enhance soft tissue healing in impaired healing states.

TRANSFORMING GROWTH FACTOR BETA

Transforming growth factor beta is a protein consisting of two identical polypeptide chains. It is found in kidney, placenta, blood platelets, and tumors, and has a molecular weight of 25,000. The TGF-β receptors are very specific, high-affinity receptors that are present on almost all cells. In platelets, TGF-β is present in large quantities relative to its presence in other cells, suggesting its role in wound healing, vessel wall maintenance, and thrombogenesis.[6]

The paradoxical action of TGF-β is that it inhibits vascular cell proliferation in vitro but stimulates angiogenesis in vivo.[11] Thus, it is thought to have a functional role in regulating cell growth and angiogenesis. In the wound healing process, TGF-β may activate macrophages to release angiogenic growth factors (such as basic FGF). As these macrophage products decrease, TGF-β may then suppress further endothelial cell proliferation and coordinate vascularization for successful wound repair.[12]

Transforming growth factor beta may stimulate or inhibit cell growth, depending on the cell type and culture conditions. In connective tissue, TGF-β stimulates the formation of collagen, glycosaminoglycans, and fibronectin.[11] In vitro, TGF-β can control the effects of other peptide growth factors (basic FGF, PDGF, TGF-α, and EGF), in either a positive or negative manner.[13]

Studies in Animal Models. In vivo studies of TGF-β have yielded promising results. When applied to linear incisions, TGF-β accelerated the incisional breaking strength in rats 3 days ahead of controls. At TGF-β injection sites, marked increases of collagen, mononuclear cells, and fibroblasts were observed.[14] When topically applied to porcine skin wounds, TGF-β increased angiogenesis, connective tissue volume, and collagen content. However, TGF-β also enhanced inflammation and caused abnormal epithelial differentiation (dyskeratosis).[15]

In the impaired healing model, TGF-β was the most effective growth factor tested among EGF and PDGF in increasing collagen content in Adriamycin-treated rats. The combination of EGF, PDGF, and TGF-β led to an almost complete reversal of Adriamycin inhibition in the impaired wound healing model.[16] In diabetic-induced rats given streptozocin, TGF-β in implanted sponges increased collagen deposition, but did not affect incision tensile strength.[10] In steroid-stressed animals, TGF-β applied to incisional wounds accelerated wound breaking strength.[17] Hence, TGF-β has become one of the more promising factors to increase collagen formation in delayed healing models.

EPIDERMAL GROWTH FACTOR

Initially described by Cohen in 1962,[18] EGF was found to stimulate precocious eyelid opening and tooth eruption in newborn mice. Epidermal growth factor was first purified from mouse submaxillary glands and later from human urine as urogastrone. The EGF polypeptide has been produced by recombinant DNA techniques. It is a single polypeptide chain with a molecular weight of 6,000.

Epidermal growth factor receptors are present on all cell membranes except for cells from the hematopoietic system. Thus, EGF has a wide range of actions, suggesting its large variety of functions in vivo. The actions of EGF are not species-specific, since epidermal and fibroblast cells from humans respond to mouse-derived EGF.[19] For EGF to elicit its effect, the target cell must be exposed to EGF for at least 5 hours.[20] Thus, repetitive or sustained administration of EGF is necessary to maximize its actions. In contrast, basic FGF, PDGF, and TGF-β require only a single dose to induce their effects.[6,14,21]

Studies in Animal Models. Having noted the tendency of animals to lick open wounds and realizing that EGF levels are high in saliva, investigators examined the effects of EGF on open wounds in 1979.[22] By removing mouse submandibular glands, which synthesize and secrete high levels of EGF, a reduced rate of spontaneous closure in full-thickness wounds occurred. Either repeated topical application of mouse EGF or communal licking of the wounds promoted wound closure.[23]

In porcine partial-thickness wounds, EGF applied topically significantly accelerated epithelialization. It also produced a marked increase in cellularity and thickness in the neodermis. The formation of granulation tissue thickness appeared dose-dependent.[24] In granulation tissue models of wound repair, sustained-release EGF increased neovascularization and the accumulation of collagen.[25] Incisional wounds treated with EGF have also been shown to increase tensile strength.[26] In the impaired healing model, EGF prevented steroid inhibition of granulation tissue in rat wound chambers.[27] Since EGF was the first angiogenic growth factor discovered, it is one of the most extensively studied and tested growth factors in animal models.

PLATELET-DERIVED GROWTH FACTOR

Platelet-derived growth factor is a basic polypeptide with a molecular weight of 30,000. It comprises two different peptide chains. This growth factor is stored in the alpha granules of blood platelets and is released at wound sites during the clotting process.[8] Infiltrating macrophages can also synthesize PDGF.[15] The PDGF receptor is present on fibroblasts, glial cells, and vascular smooth muscle cells. The receptor specifically binds to PDGF and to no other growth factor.

Platelet-derived growth factor has a number of biologic effects. It is a potent mitogen for cells of mesenchymal origin, such as fibroblasts and smooth muscle cells. Platelet-derived growth factor is thought to induce angiogenesis in vivo by activating macrophages to synthesize basic FGF or TGF-β, which, ultimately, can replicate endothelial cells.[28] Thus, it has been generally believed that PDGF has no direct action on endothelial cells in vitro. However, recent data suggest there may be PDGF receptors on some vascular endothelial cells.[29] In its actions, PDGF has been found to act synergistically with other growth factors.[16]

Studies in Animal Models. In experimental animal wounds, locally applied PDGF accelerated recruitment of macrophages and caused them to increase synthesis of the macrophage-derived growth factors (bFGF and TGF-β).[28] When PDGF was applied to incisional wounds, it accelerated the rate of wound healing by increasing wound breaking strength.[21] By enhancing fibroblast recruitment and activation, PDGF also increased granulation tissue formation and extracellular matrix. Macrophages were shown to mediate the effect of PDGF by demonstrating that rat skin incisions lacking macrophages had no difference in wound breaking strength between PDGF-treated and control incisions.[21] In diabetic rats, PDGF and insulin stimulated a more rapid increase in collagen deposition than PDGF alone.[30] Thus, various forms of defective healing may require a number of growth factors and cofactors for optimal healing.

HUMAN CLINICAL TRIALS WITH ANGIOGENIC GROWTH FACTORS

In human clinical trials, EGF has received the most attention among the purified angiogenic growth factors studied. Currently, EGF is being tested in humans to help repair cornea defects, treat nonhealing epidermal ulcers, and accelerate the healing of skin graft donor sites.[31]

In one clinical study of 12 patients who had paired skin graft donor defects, one site was treated with EGF (10 μg/mL) in combination with silver sulfadiazine, while the opposite site was treated with silver sulfadiazine alone. The results demonstrated that the EGF-treated sites had a 15% to 30% decrease in healing time due to accelerated epidermal regeneration. Histologic evaluation by punch biopsies further confirmed these results. One year after EGF therapy, biopsy specimens of these patients had no evidence of metaplasia or of hypertrophic changes.[32] In the commercial realm, EGF is actively being developed to assist healing in skin and burn wounds, corneal surface abrasions, and gastric ulcers.

In another clinical study, a mixture of platelet products was tested in 32 patients who had chronic cutaneous ulcers secondary to diabetes or chronic venous stasis. A mixture of the patient's own platelets containing five compounds (PDGF, TGF-β, platelet-derived epidermal factor, platelet factor 4, and platelet-derived angiogenesis factor) was applied to chronic skin ulcers. It was found that 81% of the treated patients and 15% of the control patients had epithelialization by 8 weeks. After crossover treatment with the platelet mixture, all of the patients had epithelialization.[33] Recently, human clinical trials using recombinant basic FGF have been started to investigate its effects on chronic cutaneous ulcers.[31]

A clinical concern in use of potent angiogenic growth factors is the possibility of permanently inducing abnormal cell transformation. In animals, histologic studies have demonstrated hyperplasia in regenerating tissue treated with EGF. However, when the EGF treatment ceased, the cellular architecture returned to normal.[32]

FUTURE POTENTIAL IN SOFT TISSUE WOUND HEALING

With cloning of polypeptide growth factors, large-scale testing of these proteins has now become possible. Since most of their half-lives are several hours or less, a sustained-release delivery system would be optimal in order to prolong their exposure to wounds and hence maximize their effect. Carriers and formulations are being investigated in the form of gels, lotions, and bandages for topical application. Slow-release formulations of EGF in multilamellar liposomes or collagen gels have shown promising results in enhancing tensile strength and wound reepithelialization.[34]

Some investigators have suggested that patients with diseases such as diabetes may have suboptimal concentrations of growth factors at the wound site. This conjecture was made from the observation that adding growth factors to wound chamber models restored the wound repair capacity in diabetic rats.[30] Thus, the use of angiogenic growth factors may improve soft tissue wound healing in patients with conditions that impair healing, such as diabetes and steroid dependency.

In the realm of skin flap and skin graft survival, in which the rate of revascularization is crucial, angiogenic growth factors delivered in sustained-release forms are promising.[9] Future goals for the use of these factors would be to improve the revascularization of skin flaps and grafts in areas of delayed neovascularization, as in irradiated regions.

In their future therapeutic applications, the administration of growth factors in combination may be more effective than the use of a single agent alone. This was suggested by the demonstration that the combination of PDGF and TGF-β stimulated higher collagen deposition than TGF-β alone in Adriamycin-treated rats.[16]

Regarding hypertrophic scarring and keloid formation, one can postulate that these phenomena are caused by an excessive presence or activity of growth factors. A relationship between excessive TGF-β production and increased target cell sensitivity may be evident in keloid formation.[35]

The use of antagonists against specific angiogenic growth factors is a possible means by which one could modify hypertrophic scarring, keloid formation, or hemangioma growth. This could be achieved by using specific monoclonal antibodies against growth factors or against the growth factor receptors. Antagonism might also be achieved by administering pharmacologic agents to modify the expression of peptide growth factors.

The role of angiogenic polypeptides is probably much more complex than the mere stimulation of target cells. Temporal and local control of wound healing may involve regulating growth factor release from several different cells (macrophages, platelets, and endothelial cells), as well as directing the interaction of growth factors among themselves.

The therapeutic applications of angiogenic growth factors in soft tissue wound healing are beginning to emerge. A major challenge in this new biochemical frontier is to determine the optimal methods and timing for delivering these angiogenic growth factors in biologically active forms.

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MEMBRANOUS CYTOPLASMIC BODIES IN THE LATERAL WALL OF THE CAT COCHLEA

KENSUKE WATANABE, MD
SAITAMA, JAPAN

ATSUSHI KOMATSUZAKI, MD
TOKYO, JAPAN

Membranous cytoplasmic bodies (MCBs) were observed both in the intermediate cells of the stria vascularis and in the fibrocytes of the spiral ligament in normal cats. The MCBs in the intermediate cells were round or ovoid, ranged from 1 to 5 μm in diameter, and consisted of 2 to 40 or more layers disposed concentrically about a core. The core was composed of not only cytoplasm but also of mitochondria in various stages of disintegration, empty vacuoles, and many kinds of dense bodies similar to lysosomes. The MCBs in the fibrocytes were similar to those in the intermediate cells, but they were a little smaller in diameter and consisted of fewer than 10 layers. Both in the intermediate cells and in the fibrocytes, MCBs seem to have a phagocytic function.

KEY WORDS — fibrocyte, intermediate cell, membranous cytoplasmic body, spiral ligament, stria vascularis.

INTRODUCTION

The stria vascularis is presumed to be an important epithelium involved in the production of endolymph[1] and in generation of the endocochlear potential.[2] It is classically described as a three-cell-layered tissue consisting of marginal, intermediate, and basal cells.[3] Of the three principal cell types, only intermediate cells have ramifying dendritic processes that come into contact with the strial capillaries.

In the course of an ultrastructural study of the lateral wall of the normal cat cochlea, membranous cytoplasmic bodies (MCBs) were observed in the intermediate cells and in the fibrocytes of the spiral ligament. These MCBs have been seen in tissues in both normal and diseased conditions. In normal tissue, MCBs have been found in dendrites of neurons in the cerebral cortex,[4] in cells of the pineal[5] and parathyroid glands,[6] and in spermatocytes[7] and oocytes.[8] In diseased tissue, MCBs have been described in the liver affected with systemic lupus erythematosus[9] and hepatoma,[10] the cerebral cortex of Alzheimer's disease[11] and infantile amaurotic idiocy,[12] and the white matter of metachromatic leukodystrophy.[13] These structures have been found in tissues with a variety of experimentally induced pathologic conditions, including hepatic cells after the administration of drugs,[14-17] and in nerve cells of the central nervous system after chronic hypoxia.[18,19] Hinojosa and Rodriguez-Echandia[20] described MCBs in the processes of the intermediate cells of the cat and termed them "concentric cisternae of smooth endoplasmic reticulum." However, they did not describe or discuss them in detail.

There is an increasing awareness of the role of the intermediate cells in the stria vascularis and the fibrocytes in the spiral ligament in water and electrolyte transport.[21] In the present report we describe the ultrastructural features of MCBs in the lateral wall of the cochlea and discuss the presumed functions of the intermediate cells and fibrocytes.

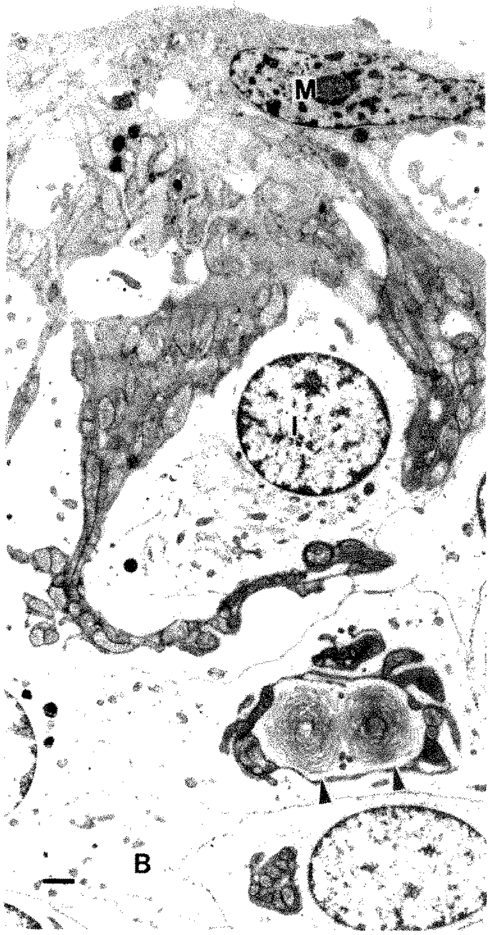

Fig 1. Membranous cytoplasmic bodies (arrowheads) are observed in processes of intermediate cells (I), which were surrounded by marginal cells (M). B — basal cell, bar — 1 μm.

From the Department of Otolaryngology, Tokyo Medical and Dental University, Tokyo, Japan.

REPRINTS — Kensuke Watanabe, MD, Dept of Otolaryngology, Dokkyo University School of Medicine, Koshigaya Hospital, 2-1-50, Minamikoshigaya Koshigaya-shi, Saitama 343, Japan.

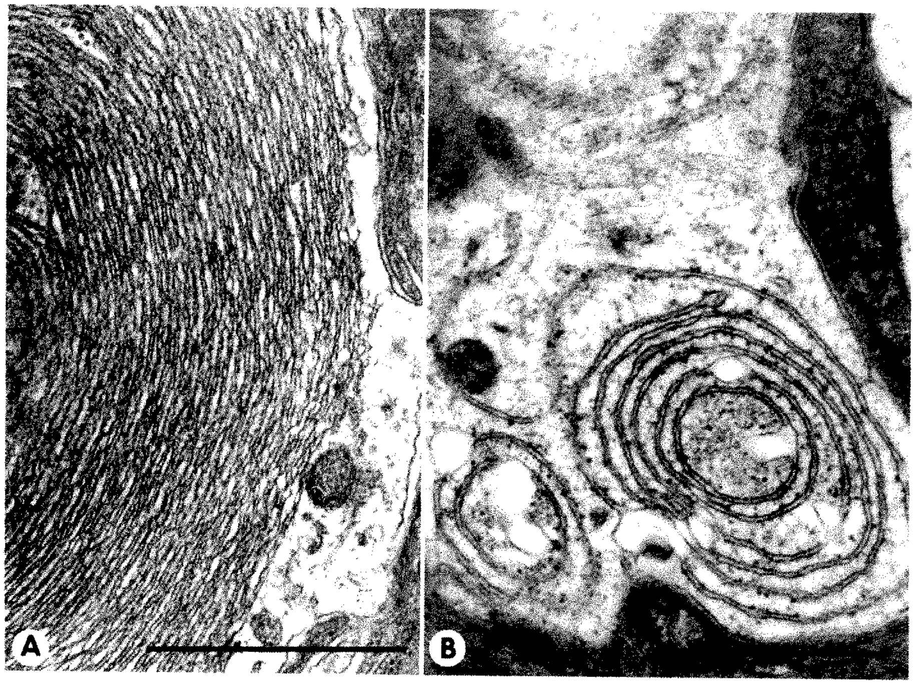

Fig 2. Bars — 1 μm. A) Lamellae consist of double-layered membranes without ribosomes. B) Layers of membrane are loosely disposed. Ribosomes are attached to membrane at sporadic intervals.

MATERIALS AND METHODS

Five cats weighing 3 to 3.5 kg were anesthetized with an intraperitoneal injection of pentobarbital (50 mg/kg). They were painlessly killed by perfusion through the left ventricle with 2% glutaraldehyde buffered with a 0.1 mol/L cacodylate for 1 hour. Microdissection was performed to separate the lateral wall of the cochlea from the second turn of the cochlea. These samples were further fixed for 1 hour with 2% glutaraldehyde and then washed three times with 0.1 mol/L cacodylate buffer (containing 8% sucrose, pH 7.2). They were then postfixed in 1% osmium tetroxide buffered with 0.1 mol/L cacodylate and embedded in Epon 812. Ultrathin sections were cut on a Porter Blum type II ultramicrotome and examined by transmission electron microscopy.

RESULTS

Stria Vascularis. At low magnification, the three strial cell types were distinguished: marginal, intermediate, and basal (Fig 1). Some MCBs were observed in all five cats and generally were observed in the peripheral portions and processes of the intermediate cells (Fig 1, arrowheads), which were surrounded by the processes of the marginal cells. In some cases the processes of the intermediate cells in which MCBs were contained protruded into the bodies of the basal cells. The MCBs were round or ovoid and ranged from 1 to 5 μm in diameter. The bodies consisted of 2 to 40 or more layers of membranes disposed concentrically about a core. The structures revealed no evidence of a delimiting membrane separating the MCBs from the adjacent cytoplasm (Figs 2 and 3A,B). The lamellae consisted of double-layered membranes, each possessing a regular width of 20 nm (Fig 2A).

The composition of the core varied with the MCB. For example, cores were formed by one or more mitochondria in different stages of disintegration (Fig 3A,B), empty vacuoles (Fig 3A), many dense bodies similar to lysosomes (Fig 3B), and several other organelles. These organelles occasionally appeared between the sheets of membranes (Fig 3B). Some MCBs had lost most of their lamellar configuration and appeared either granular or as dense masses of amorphous material (Fig 3A). In a few cases, MCBs were observed in the body of the intermediate cells (Fig 3C). Although the characteristics of MCBs near the nucleus were almost the same as those within the processes of the intermediate cells, the membranes were arranged more loosely at the MCBs' periphery (Fig 3C, inset).

Although particles were occasionally observed attached to the membranes (Fig 2B) and peripheral cisternae occasionally exhibited short strips of attached particles (Fig 3C, inset), these lamellar formations were generally smooth-surfaced.

Spiral Ligament. Some MCBs were also observed in the fibrocytes that were in the spiral ligament (Fig 4). The MCBs in the fibrocytes were generally smaller than those in the intermediate cells (Fig 4). They ranged from 1 to 2.5 μm in diameter. The bodies consisted of fewer than 10 layers of cisternae. The core was almost the same as in the intermediate cells.

DISCUSSION

Biochemical analysis of the endolymph reveals that it contains an unusually high concentration of potassium and a low concentration of sodium.[22,23]

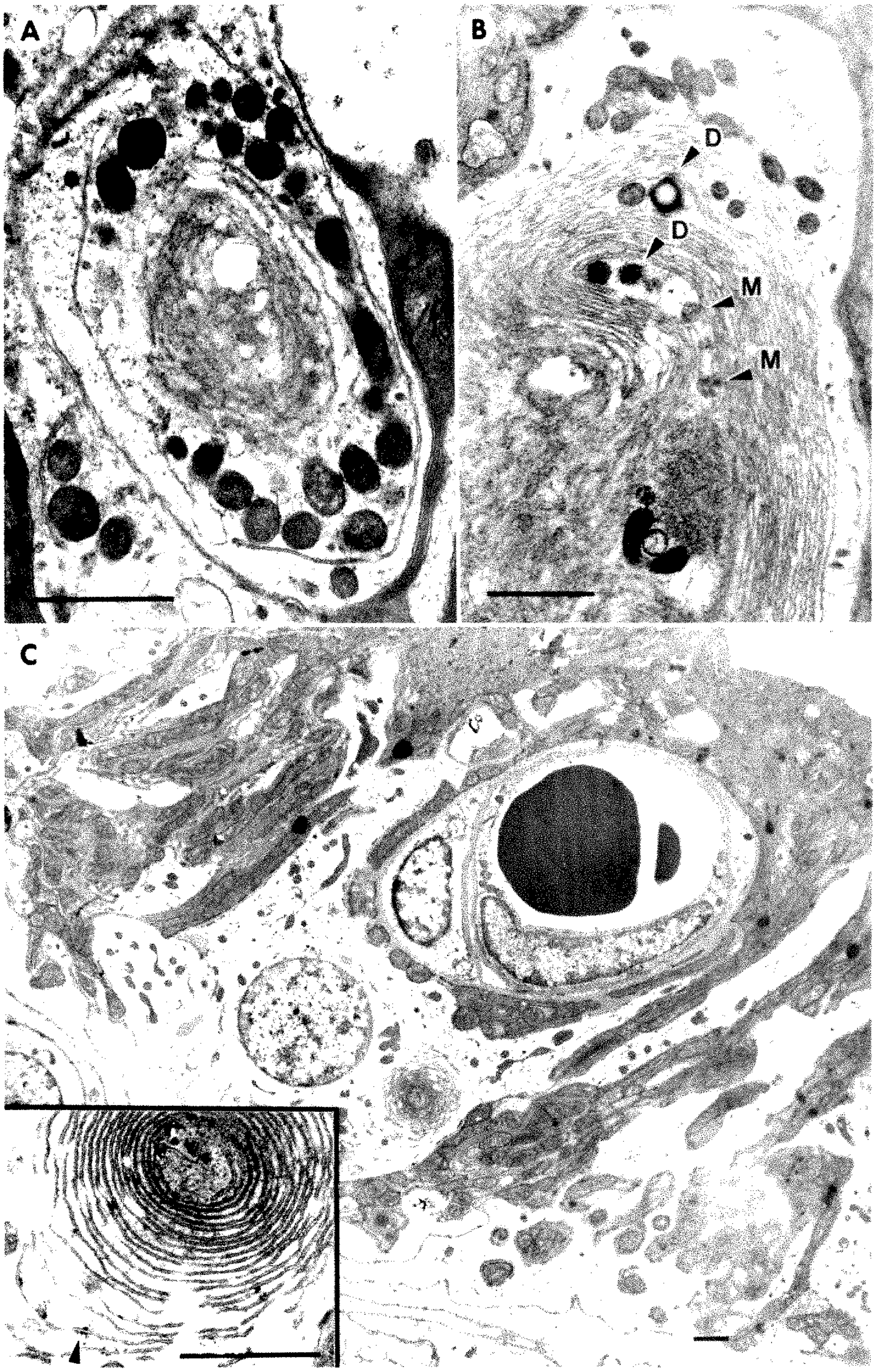

Fig 3. Bars — 1 μm. A) Most of lamellar configuration is lost and membranous cytoplasmic body appears as dense mass of amorphous material. Many mitochondria are observed between this dense mass and outermost layer. Empty vacuoles are observed in core. B) Degenerating mitochondra (M) are observed in core. Dense bodies (D) similar to lysosomes are also observed in core and between membranes. C) Membranous cytoplasmic bodies are infrequently observed in body of intermediate cell. Inset) Higher magnification of body in C. Membranes are arranged more loosely at periphery, where ribosomes are attached to membrane (arrowhead).

The concentration of cations of the endolymph is actively regulated by some of the epithelial structures lining the cochlear duct.[24] Hinojosa and Rodriguez-Echandia[20] suggested that by its location and fine structural differentiation, the marginal cell of the stria vascularis is best adapted to accomplish this function. However, carbonic anhydrase, which is thought to play an important role in homeostatic mechanisms in the endolymph, is localized not only on the membranes of the marginal cells but also in the cytoplasm of the intermediate cells, especially in their processes.[21] Therefore, the intermediate cells are presumed to take an active part in both fluid and electrolyte transport in addition to the marginal cells.

It is also interesting that carbonic anhydrase is observed in the fibrocytes of the spiral ligament. This finding suggests that the fibrocytes also have an ion transport function.[21] Kimura and Schuknecht[25] also reported the similarity between human intermediate cells and fibrocytes in that

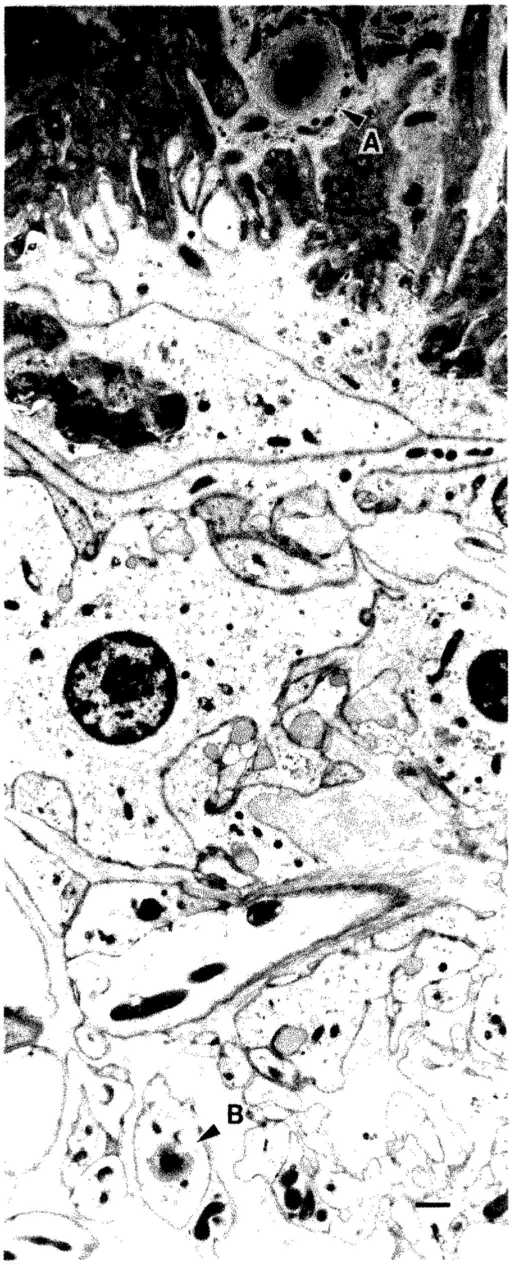

Fig 4. Membranous cytoplasmic bodies are observed both in intermediate cell (A) and in fibrocyte (B).

smooth endoplasmic reticula are found in both cell types. They suggested that both cells were secretory. In the present study, MCBs were also observed both in the intermediate cells and in the fibrocytes. It is possible that the functions of both cell types are similar.

Lamellar formations similar to MCBs have been described by many investigators. However, relationships of the membranous bodies to the rough- or smooth-surfaced elements of the endoplasmic reticulum are not constant. In many instances, the lamellar formations have been linked with the rough-surfaced cisternae,[14,15] but in others they have been connected with the smooth-surfaced profiles.[26] The membrane-associated particles are thought to be ribosomes.[9]

In the present study, MCBs generally consisted of smooth-surfaced membranes, but in a few MCBs, rough-surfaced membranes were observed (Fig 2B). Moreover, while the lamellar formations were generally smooth-surfaced, the peripheral cisternae of MCBs occasionally exhibited short strips of attached ribosomes (Fig 3C).

The functional significance of MCBs may be one or more of the following. They may signify degenerative alterations of the endoplasmic reticulum. In studies of hypoxic nerve cells of the central nervous system[19] and in liver cells after exposure to toxic agents,[15] this interpretation has been favored. They may represent generative or regenerative formations of endoplasmic reticulum.[9,16] They may represent autophagic vacuoles because of the occurrence of altered mitochondria and lipid bodies within the core of MCBs.[14] Herdson et al[14] have suggested the possibility that MCBs might be concerned with detoxification. Fawcett and Wilson[10] have also demonstrated viruslike particles within the core of MCBs from tissue cultures on mammary carcinomas.

In the present study, MCBs contained mitochondria in different stages of disintegration and many kinds of dense bodies and empty vacuoles in the core. Therefore, it seems more reasonable to relate the MCBs of the cat intermediate cells to phagocytosis rather than to degenerative alterations or regenerative formation. It was reported that the dense vacuoles of the intermediate cells contain iron, which can be sequestered from dying erythrocytes in mice[27] and autophagocytosed melanin in chinchillas.[28] These reports have also demonstrated the phagocytotic activity of the intermediate cells.

It is possible that the intermediate cells have phagocytic functions in addition to fluid and electrolyte transport and that the fibrocytes also have the same functions. The MCBs seem to be a special formation showing phagocytosis only in the cat.

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IMAGING CASE STUDY OF THE MONTH

VAGAL SCHWANNOMA

ROBERT J. SCHMALL, MD KENNETH D. DOLAN, MD

IOWA CITY, IOWA

INTRODUCTION

Many lesions can produce vagal neuropathy, and all can present similar clinical symptoms. Hoarseness is one of the common presentations suggesting vagal neuropathy. Among the causes of vagal neuropathy, a neuroma or a schwannoma of the vagal nerve can cause symptoms attributed to neuropathy of cranial nerves IX, XI, and XII, as well as cranial nerve X. If a vagal neuroma or schwannoma is large enough and it is in a vulnerable location, such as the jugular foramen, it can affect the surrounding nerves by compressing them. The compressive effects can produce significant clinical disease, depending on the severity and duration of compression.

Magnetic resonance imaging (MRI) and computed tomography (CT) are useful in both the detection of cranial nerve disease and the suggestion of a likely diagnosis. The use of MRI and CT in evaluation of a patient with clinical signs suggestive of multiple cranial nerve disease is discussed.

CLINICAL FINDINGS

A 68-year-old man first presented with recent onset of left-sided tongue weakness of undetermined cause. One year later he returned with a new onset of hoarseness that had stabilized over the preceding months. An initial otolaryngology examination showed left vocal cord paresis without associated palatal or pharyngeal weakness. The patient's hoarseness worsened and he developed increased left vocal cord paresis as shown in a subsequent clinical examination. The examination also showed a progressive left-sided tongue atrophy associated with the original weakness, left suprascapular atrophy, a decreased gag reflex on the left, and no soft palate elevation on the left. There were no other clinical findings that could be attributed to cranial nerves. The patient underwent both MRI and CT study and eventual excision of the lesion felt to be causing the clinical symptoms.

RADIOGRAPHIC FINDINGS

Tongue atrophy is reflected in the CT examination by low density produced by fatty infiltration of the muscles involved (Fig 1A). A low-density mass was present in the region of the left skull base just below the jugular foramen. The mass was located between the carotid artery and the jugular vein and seemed to displace and separate both vessels (Fig 1B). A CT view through the left jugular bulb revealed a lucent mass filling the bulb. The jugular vein was not visible (Fig 1C).

Magnetic resonance imaging studies of the lesion were also performed. A T1 view through the jugular bulb area demonstrated a low-signal mass filling the area of the bulb (Fig 2A). After gadolinium enhancement, the mass had bright signal on the T1 examination (Fig 2B). Bright signal characterized the mass on T2 axial (Fig 2C) and coronal (Fig 2D) studies. The signal characteristics most strongly suggested a neuroma (schwannoma), while the mass location and clinical findings suggested that the lesion was vagal in origin.

SURGICAL FINDINGS

An infratemporal fossa approach was used to visualize the lesion. The lesion appeared to be a nerve X neuroma that had intracranial extension. A pathologic examination determined the diagnosis of a nerve X schwannoma, although no classic Verocay bodies were seen.

DISCUSSION

The MRI findings presented here show a significant lesion of cranial nerve X in the area of the jugular foramen. At this level it could easily affect nerves IX, XI, and XII owing to their proximity to nerve X. This would explain the other clinical findings not directly related to the vagal nerve, such as weakness and atrophy of the left side of the tongue, which is supplied by the hypoglossal nerve. This atrophy is clearly demonstrated in the CT image (Fig 1A). This would also explain the suprascapular atrophy due to compression of the spinal accessory nerve.

The ability to identify all of the cranial nerves during routine MRI of the head was demonstrated by Castillo et al.[1] They described a systematic approach for evaluation of the peripheral cranial

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From the Department of Radiology, The University of Iowa College of Medicine, Iowa City, Iowa.

REPRINTS — Kenneth D. Dolan, MD, Dept of Radiology, The University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

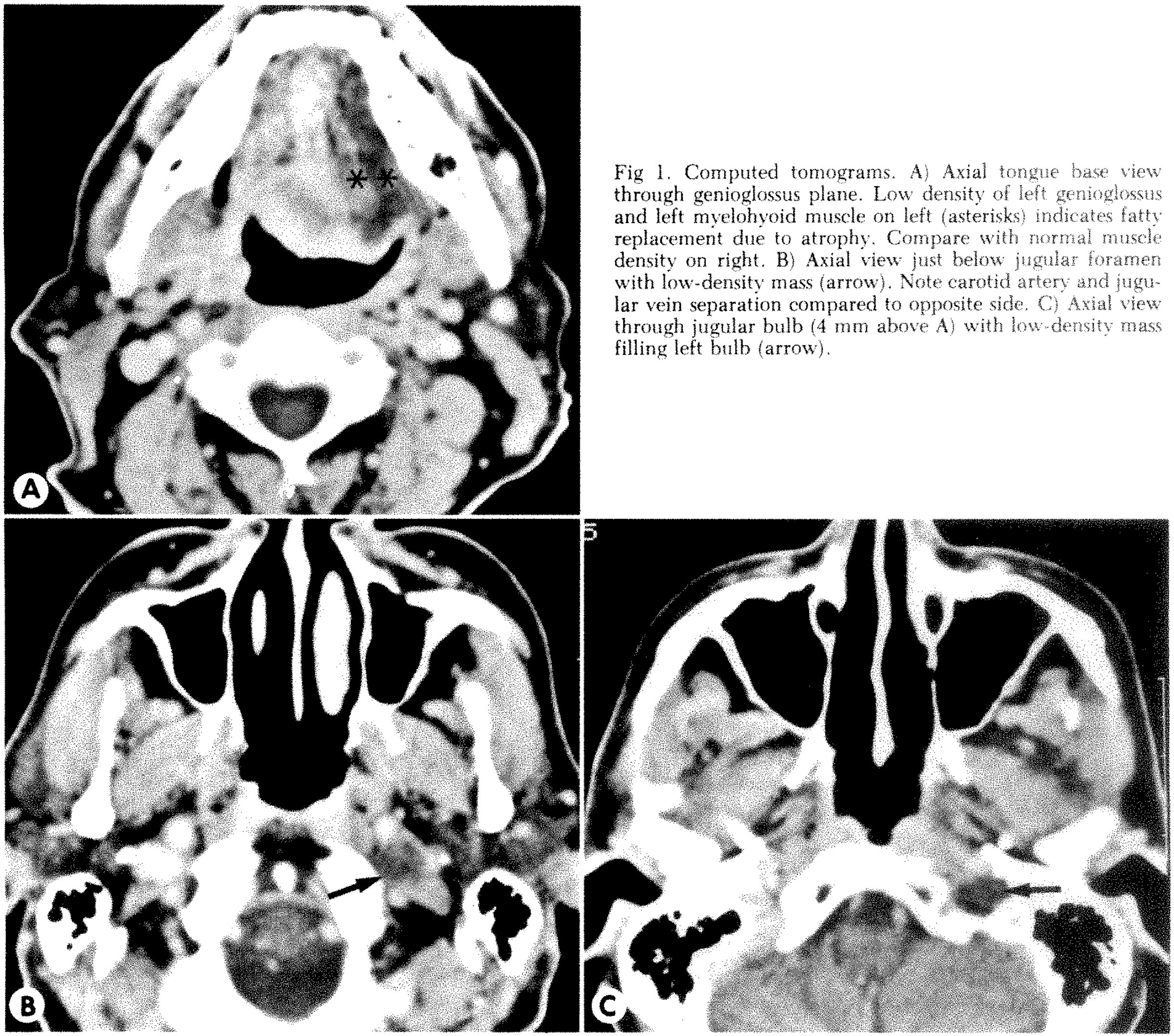

Fig 1. Computed tomograms. A) Axial tongue base view through genioglossus plane. Low density of left genioglossus and left myelohyoid muscle on left (asterisks) indicates fatty replacement due to atrophy. Compare with normal muscle density on right. B) Axial view just below jugular foramen with low-density mass (arrow). Note carotid artery and jugular vein separation compared to opposite side. C) Axial view through jugular bulb (4 mm above A) with low-density mass filling left bulb (arrow).

nerves. Each of the cranial nerves can be visualized with use of the proper MRI projection. The vagus nerve, particularly important in this case, can be identified clearly with MRI.

The anatomy around the jugular foramen is also quite important in our case. The use of MRI to study this area was described by Daniels et al.[2] Magnetic resonance images of five normal individuals were compared to the photographs of prepared cadaver slices through the jugular foramen. Magnetic resonance imaging of the jugular foramen was found to be particularly useful owing to the lack of signal from flowing blood and bone. This would make it easier to identify the nerves coursing through the foramen. The anatomy of nerves IX, X, and XI in the jugular foramen can be successfully demonstrated.[2] Nerve XII, close to the jugular foramen, can also be seen with MRI.[1] Changes in the anatomy around the jugular foramen, similar to those created by a neuroma or schwannoma, are readily identified in the images presented here.

Evaluation of isolated vagal neuropathy was described by Jacobs et al.[3] They described a protocol for the examination of nerve X by CT and MRI. The imaging protocol and the algorithm they developed were based on defining the lesions of the vagus nerve as proximal or distal. A proximal lesion is one located between the brain stem and the oropharynx, and a distal lesion is one found between the hyoid bone and the mediastinum. A retrospective analysis was performed on 48 patients with vagal neuropathy. The study suggested that the optimal imaging tool for proximal lesions is MRI, and the optimal tool for imaging distal lesions is CT. In a hoarse patient, such as the one in this case, the first step in the diagnostic algorithm is to examine the vocal cords. If this examination is negative for local disease and there are no palpable neck masses, further examination is necessary. Jacobs et al suggest MRI if a proximal lesion is suspected. Chest radiography and then CT are suggested if a distal lesion is suspected, although enhanced MRI may be used as an alternative to CT.

Our patient does not fit perfectly into the diagnostic algorithm, because his initial presenting symptom was tongue weakness on the left side, but he subsequently developed hoarseness. When no local

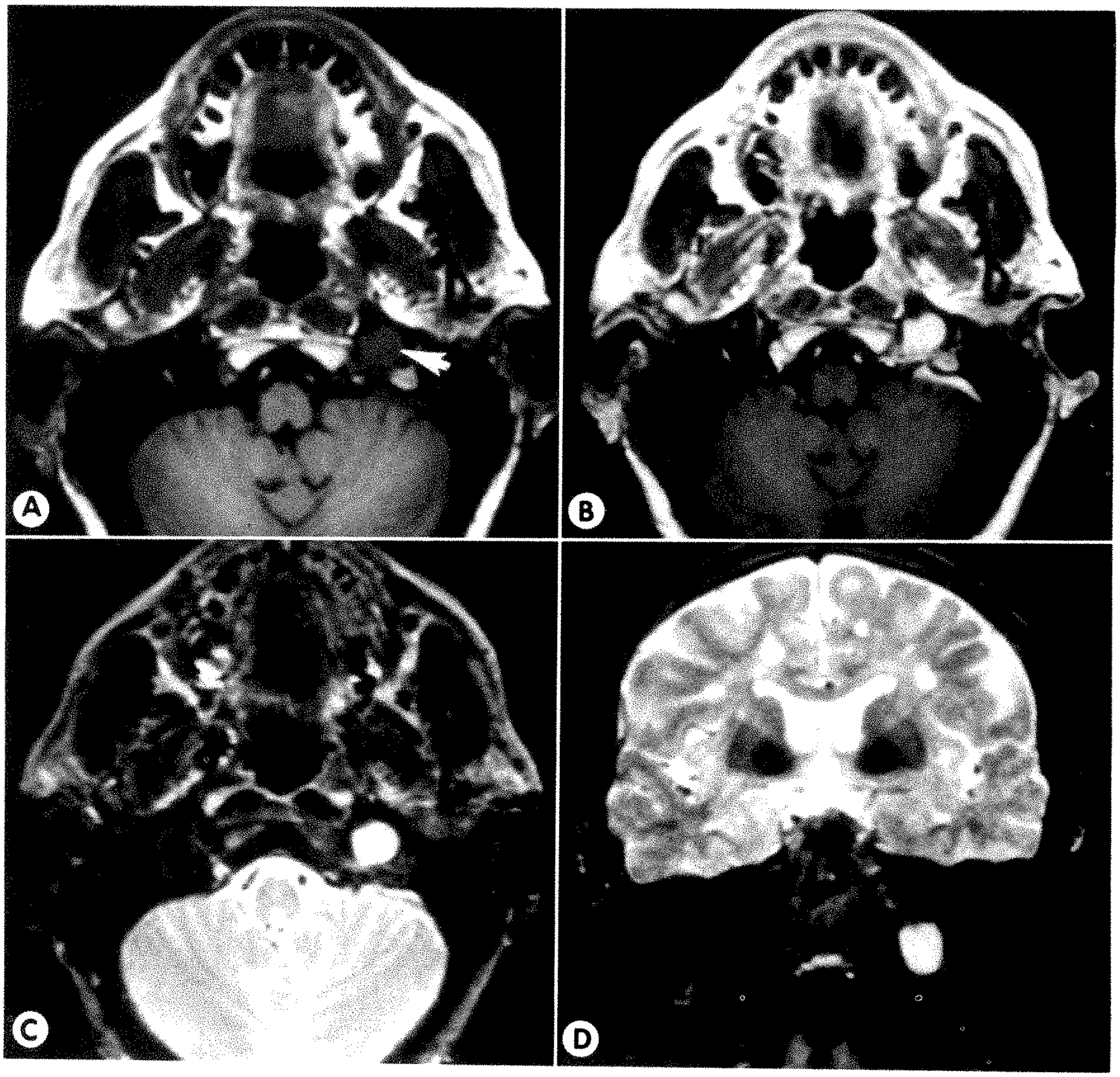

Fig 2. Magnetic resonance images. A) T1 (TR 650/TE 20) view at jugular bulb plane with low signal mass (arrow). B) T1 (TR 650/TE 20) view, same level as in A after gadolinium, showing mass enhancement. C) T2 (TR 2,100/TE 90) axial view in same plane with bright signal in jugular bulb mass. D) T2 (TR 2,100/TE 90) coronal view showing vertical dimension and appearance of mass with bright signal.

vocal cord lesion was found and multiple cranial nerve neuropathies were beginning to develop, a lesion at the level of the jugular foramen was suspected. Magnetic resonance imaging and CT were effective means of detection and localization of the abnormality.

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IMAGING CASE STUDY OF THE MONTH

NONINVASIVE RADIOLOGIC OPTIONS IN EVALUATING INTRACRANIAL COMPLICATIONS OF OTITIS MEDIA

ERIC H. STEIN, MD
MICHAEL J. CUNNINGHAM, MD
ALFRED L. WEBER, MD
BOSTON, MASSACHUSETTS

INTRODUCTION

The widespread use of systemic antibiotic therapy has both decreased the incidence and altered the clinical presentation of the suppurative intracranial complications of otitis media.[1,2] Fewer opportunities exist for clinicians to assess the diverse radiologic options currently available for evaluating these patients. This case illustrates the use of the less invasive of these radiologic modalities. The recognition of subacute intracranial presentations, coupled with an awareness of the newer radiologic techniques available for their diagnosis, may prevent disastrous clinical consequences.

CASE PRESENTATION

A 12-year-old girl with no history of previous ear disease presented with left-sided otalgia and purulent otorrhea of 2 to 3 weeks' duration. Her left auricular and postauricular pain were increasing despite oral cefaclor therapy. She complained of decreased hearing on the left side, but denied vertigo or headache. Her medical history was otherwise noncontributory.

She was an alert, oriented, but ill-appearing girl with a temperature of 37°C. Her left ear canal was filled with thick, purulent, malodorous drainage; suctioning revealed a large aural polyp emanating from the superior aspect of her left tympanic membrane. Left postauricular swelling and erythema without fluctuation or pinna displacement was apparent. Her right ear examination showed normal findings. Bilateral posterior triangle lymphadenopathy was appreciated on neck palpation. Tuning fork examination suggested a left conductive hearing loss. Facial nerve function was intact and symmetric bilaterally. She had no nystagmus, nuchal rigidity, or focal neurologic abnormalities.

The laboratory workup was remarkable for a white blood cell count of 20,000/mm^3, including 60% segmental neutrophils and 30% band forms, hematocrit within normal limits, a negative monospot, and an erythrocyte sedimentation rate of 70 mm/h. Mastoid radiographs revealed unilateral left-sided middle ear and mastoid air cell opacification with apparent intact septae.

She was admitted with the presumptive diagnosis of left-sided otitis media and mastoiditis. Her otorrhea was cultured and treatment was begun with intravenous chloramphenicol sodium succinate and nafcillin sodium as well as topical polymyxin B sulfate–neomycin sulfate–hydrocortisone suspension. A computed tomography (CT) scan was scheduled.

Within several hours of admission, the patient became drowsy, lethargic, and confused. She experienced a convulsive episode characterized by leg tremors, nausea, and incontinence of urine. Her temperature spiked to 41.6°C. This abrupt deterioration of her mental status prompted emergent pediatric and neurosurgical consultations in addition to the performance of a contrast-enhanced CT scan of the brain and temporal bones. The CT study revealed a 1-cm-diameter epidural abscess characterized by a central area of low attenuation and a peripheral enhancing rim (Fig 1).

She underwent an immediate left cortical mastoidectomy. Dural granulation tissue within a bony dehiscence adjacent to the sigmoid sinus was discovered. The sigmoid sinus appeared normal. No pus was encountered. A left aural polypectomy and tympanotomy tube placement were also performed.

The patient defervesced immediately postoperatively and her mental status returned to normal. Cultures of the posterior fossa dura granulation tissue grew abundant anaerobic *Fusobacterium necrophorum*. Infectious disease consultation suggested continuing the intravenous nafcillin and chloramphenicol for a total of 14 days. During her 2-week course of intravenous therapy she remained afebrile, with normalization of her total white blood cell count and differential. Her erythrocyte sedimentation rate, however, remained elevated in the

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From the Departments of Otolaryngology (Stein, Cunningham) and Radiology (Weber), Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts.

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REPRINTS — Michael J. Cunningham, MD, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114.

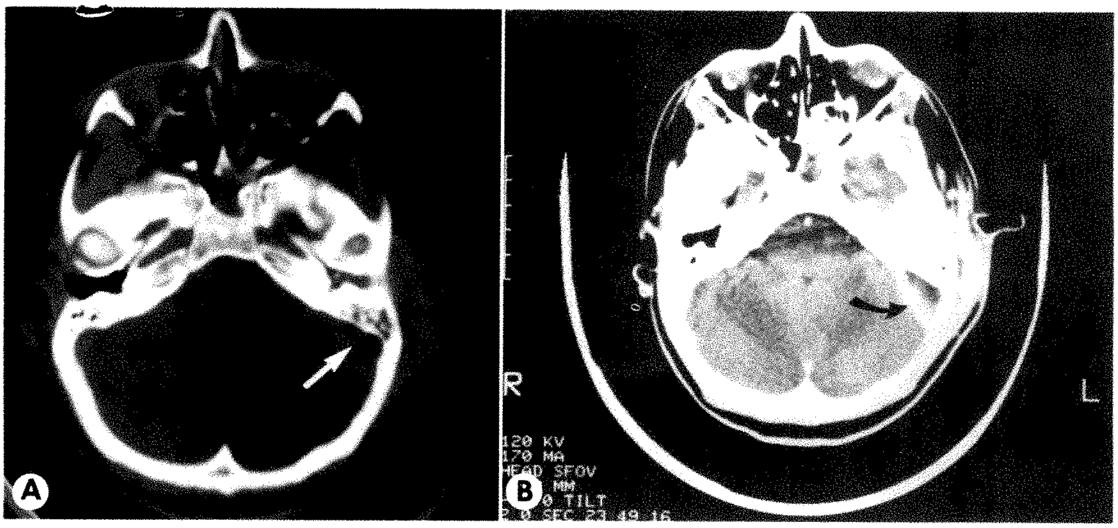

Fig 1. Computed tomograms revealing 1-cm-diameter epidural abscess reflected by central area of low attenuation and peripheral enhancing rim. Arrows — medial rim of abscess. A) Bone window. B) Soft tissue window.

50- to 70-mm/h range. A postoperative audiogram revealed her right-ear speech reception threshold to be 5 dB, in contrast to an elevated left-ear threshold of 35 dB; this loss was entirely conductive, with an excellent discrimination score of 98%.

On the 14th postoperative day, her temperature again abruptly spiked to 39.7°C with no associated changes in mental status. Her left otologic examination revealed a dry, patent tympanotomy tube. She had no postauricular erythema or fluctuance and a negative Griesinger's sign. She did, however, demonstrate an acute increase in her left postauricular and anterior cervical lymphadenopathy. No associated axillary or inguinal nodes were palpated. Findings on neurologic examination remained normal and her eye examination showed no chemosis or papilledema. Her white blood cell count was stable at 6,700/mm^3, but a marked bandemia, including 39% segmented neutrophils and 39% band forms, was noted. Her erythrocyte sedimentation rate remained elevated at 51 mm/h. Hematocrit remained unchanged.

A contrast-enhanced CT scan revealed the surgical defect in the posteromedial mastoid cortex with enhancement of adjacent dura but no evidence of residual abscess or dural sinus thrombosis (Fig 2). The patient, however, continued to spike twice-daily temperatures in the 38°C to 39°C range.

A radiologic consultation was requested as to the most appropriate study to elucidate the suspected diagnosis of sigmoid sinus thrombophlebitis. A nuclear medicine radionuclide brain flow study and a magnetic resonance imaging (MRI) scan were recommended in preference to a more invasive digital subtraction angiogram. The nuclear medicine flow study revealed marked asymmetry in the venous phase with no evidence of activity in the lateral portion of the left transverse sinus, sigmoid sinus, or upper jugular vein (Fig 3). An MRI scan with flow parameters confirmed these findings. An axial 4-mm gradient echo image revealed normal flow on the right, reflected by increased signal intensity in the transverse sinus and in the jugular bulb. No flow was detected on the left side (Fig 4A). A coronal 4-mm gradient echo section also demonstrated blood flow in the right jugular bulb and vein, while no flow was observed on the left side (Fig 4B). These complementary studies both suggested thrombosis of the left sigmoid-transverse sinus with possible clot propagation into the left jugular vein, supporting the clinical diagnosis of septic thrombophlebitis.

The neurosurgical consultant thought that the patient demonstrated no signs or symptoms suggestive of meningitis or intradural extension of the initial epidural process. The pediatric infectious disease consultant found no evidence of septic emboli clinically or on chest radiographs. A joint decision was made to closely observe the patient on a new intravenous antibiotic regimen of metronidazole and

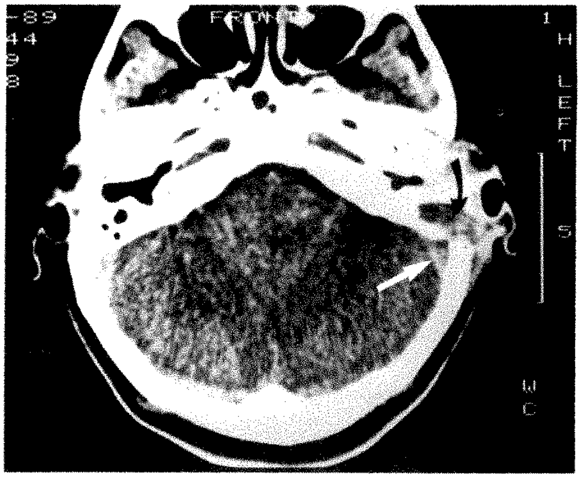

Fig 2. Computed tomogram with contrast showing surgical defect (black arrow) with enhancement of adjacent dura (white arrow) but no evidence of residual abscess or dural sinus thrombosis.

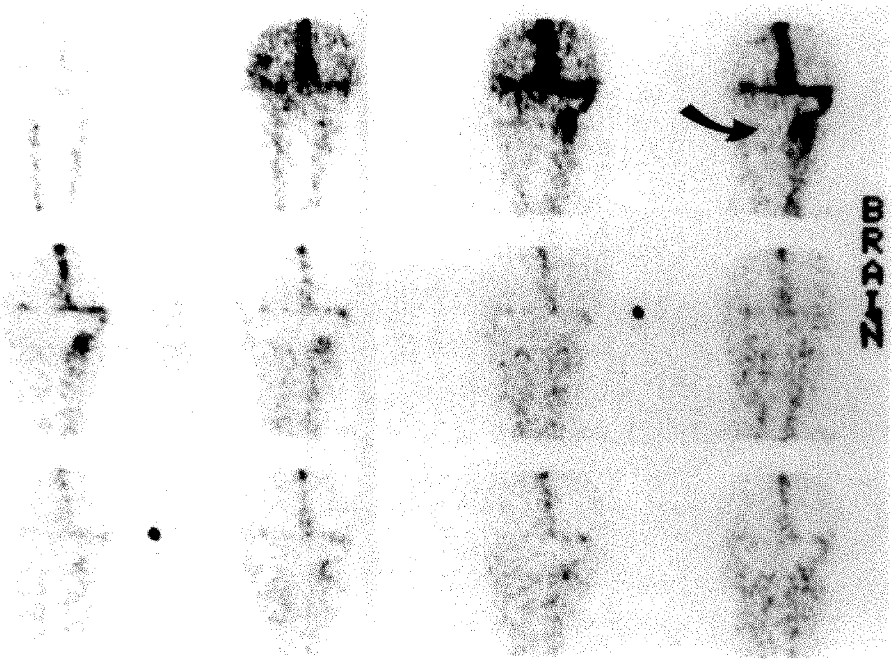

Fig 3. Radionuclide brain flow study, posterior-anterior view, demonstrating marked asymmetry in venous phase with no evidence of activity in lateral portion of left transverse sinus, sigmoid sinus, or upper jugular vein. Arrow — lack of activity in thrombosed vasculature.

cefuroxime sodium rather than proceeding with surgical exploration of the sinus.

The patient defervesced after 2 days and remained afebrile without otologic or systemic symptoms during an additional 14 days of intravenous therapy. She was discharged on a regimen of amoxicillin-clavulanate potassium for an additional 21 days. Her white blood cell differential returned to normal and her erythrocyte sedimentation rate decreased dramatically to 8 mm/h at the completion of therapy. She remains asymptomatic now, 18 months after treatment.

DISCUSSION

This case illustrates the use of the less invasive radiologic options available for the diagnosis of suspected intracranial complications of suppurative otitis media. Computed tomography with contrast infusion is often regarded as the radiologic study of choice for such diagnostic purposes.[3-5] Computed tomography alone can often identify extradural, subdural, and brain abscesses, as well as provide supportive evidence of sigmoid sinus thrombosis and cerebritis. In patients with signs and symptoms of meningeal irritation, a CT scan prior to lumbar puncture can also provide critical information concerning hydrocephalus or abscess or mass effect, thereby greatly influencing therapeutic intervention.

In this case, the initial CT proved particularly valuable in its clear delineation of an extradural pathologic process; however, it failed to reveal a clinically suspected thrombosis of the dural sinuses. This failure of CT to delineate dural sinus thrombosis has been noted by others and is usually attributed to the close proximity of dense bony structures that may cause artifacts on partial volume averaging.[6,7] The detection of dural sinus thrombosis requires strong clinical suspicion and instruction of the imaging team to take special measures including precise orientation of thin cuts, concentrated contrast medium, multiplanar reconstruction, and special window settings. Computed tomography often will miss dural thrombosis when it is used as a general screen for otologic intracranial disease.[6,8,9]

The abrupt onset of spiking fevers in this case led to the search for further intracranial complication, specifically sigmoid sinus thrombophlebitis. Since the CT scan failed to clearly reveal additional disease, other diagnostic options were sought.

Clinical tests performed during lumbar puncture, such as the Queckenstedt-Stookey and Tobey-Ayer tests, are unreliable and often dangerous.[2,10]

Arteriography, retrograde jugulography, and digital subtraction venography are relatively definitive diagnostic procedures, but are invasive and risk further vascular injury.[5] Also, the use of contrast enhancement is potentially dangerous, since it may lead to dehydration and thus aggravate a hypercoagulable state.[6]

As illustrated in our case presentation, a radionuclide brain flow study can reveal dural venous asymmetry suggestive of thrombosis.[11] However, the reliability of radionuclide imaging in the detection of early disease remains uncertain.[6]

Magnetic resonance imaging is also noninvasive and has the additional benefit of using no ionizing radiation. High signal intensity on T1- and T2-weighted images indicates venous thrombosis. Gradient echo images can also be obtained to evaluate blood flow through both the arterial and venous systems.[12] As demonstrated in this case, no flow is

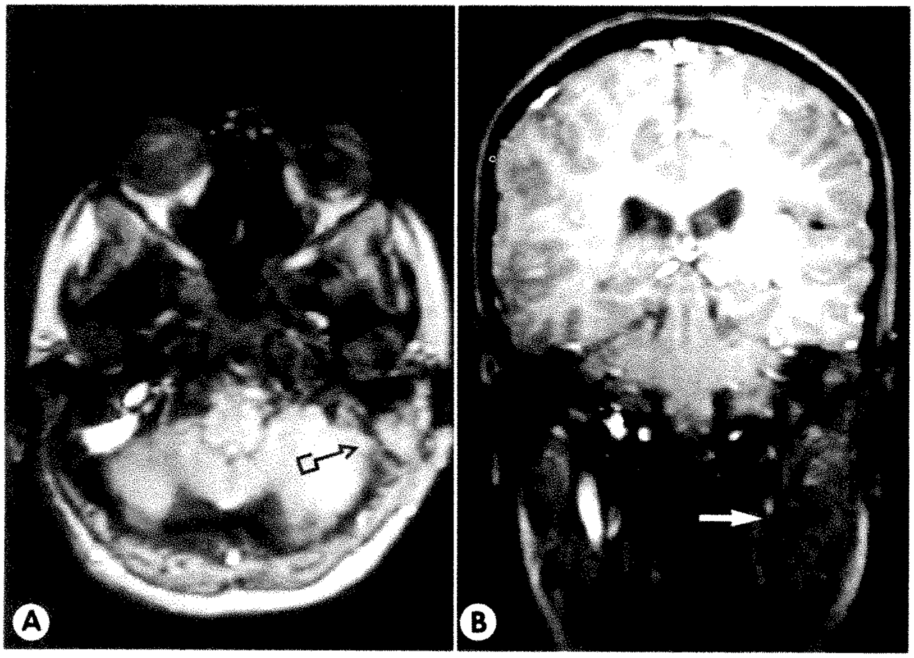

Fig 4. Magnetic resonance imaging scan with flow parameters confirming thrombotic process. A) Axial 4-mm gradient echo image reveals normal flow on right, reflected by increased signal intensity in transverse sinus and in jugular bulb. No flow is detected on left side (arrow). B) Coronal 4-mm gradient echo section demonstrates blood flow in right jugular bulb and vein. Again, no flow is observed on left side (arrow).

visible when thrombosis obliterates the vessel lumen. For these reasons MRI appears to be the imaging method of choice in patients suspected of having dural sinus and/or jugular vein thrombosis.[6,13,14]

CONCLUSION

Fortunately, new, noninvasive, radiologic techniques are currently available to assist the clinician attempting to diagnose and define otogenic intracranial complications. Magnetic resonance imaging and nuclear medicine radionuclide flow studies can be used to complement contrast-enhanced CT in detecting suspected suppurative complications. These studies may prove to be of particular value in the diagnosis of sigmoid sinus thrombophlebitis, as illustrated in this case presentation.

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PATHOLOGY CONSULTATION

SYNOVIAL SARCOMAS OF THE HEAD AND NECK

ROSARIO CARRILLO, MD
JOSE LUIS RODRIGUEZ-PERALTO, MD
JOHN G. BATSAKIS, MD
HOUSTON, TEXAS

Springing from mesenchyme rather than mature synovial tissues, synovial sarcomas are high-grade neoplasms that express epithelial as well as supporting tissue features. Accordingly, their histologic phenotypes can be epithelial, stromal, or mixed. Between 3% and 10% of all synovial sarcomas originate in the head and neck, particularly from parapharyngeal sites. These is no appreciable difference in biologic activity between synovial sarcomas of the head and neck and those arising from other anatomic sites. Five-year survivals are misleadingly optimistic and do not adequately reflect the natural history of the sarcoma. Synovial sarcoma is known to metastasize late, and few patients survive that event.

Synovial tissue is a modified connective tissue that is formed from a development of cavities in preexisting mesenchyme. The progenitor mesenchyme differentiates into two recognizable components: an inner "epithelioid" cell layer and an outer, also specialized, connective tissue layer. Committed cells from these two compartments possess properties that distinguish them from other offspring of mesenchyme, and while the cells may appear as separate entities, they are considered interchangeable.

Synovial sarcomas are not so named because they arise from fully developed and existing synovial membranes. They are malignant supporting tissue neoplasms originating from pluripotential mesenchymal cells near or even remote from articular surfaces, ie, tendons, tendon sheaths, juxta-articular membranes, and fascial aponeuroses. There is, in fact, little resemblance between normal or pathologic synovial membranes and synovial sarcoma.[1,2] There is no benign counterpart of synovial sarcoma, and at best the neoplasm is a sarcomatous caricature of synovial tissues.[3-6]

Synovial sarcomas comprise 8% to 10% of all soft tissue sarcomas, and it is estimated that between 3% and 10% of the sarcomas arise in the head and neck, where they are in relation to the prevertebral areas from the skull base to the hypopharynx, in the parapharyngeal and retropharyngeal regions, in the neck, and in orofacial and laryngeal sites.[3] The majority are parapharyngeal, only occasionally in proximity to articulations such as the cricoarytenoid, temporomandibular, and sternoclavicular joints (Fig 1).

The neoplasms lack any distinctive gross findings and can be very deceptive in their apparent circumscription with blunt invasive margins. Microcalcifications, discernible in radiographs, can be seen in cut sections. Cutaneous or mucosal surfaces overlying the sarcomas are rarely violated, but may be part of a pedunculated mass as the neoplasms expand.

There are sufficient light- and electron-optic and immunocytochemical features to support the thesis that synovial sarcoma exists in biphasic and uniphasic cellular forms.[7-10] The biphasic form contains recognizable epithelial and sarcomatous components. The uniphasic form manifests only the sarcoma or, rarely, only epithelial features.[10] The relative frequency of each form depends on the diligence of the search for the complementary tissue component. In that respect, we agree with Wick et al[8] that the monophasic synovial sarcoma is one of the most frequently missed and misdiagnosed soft tissue tumors.

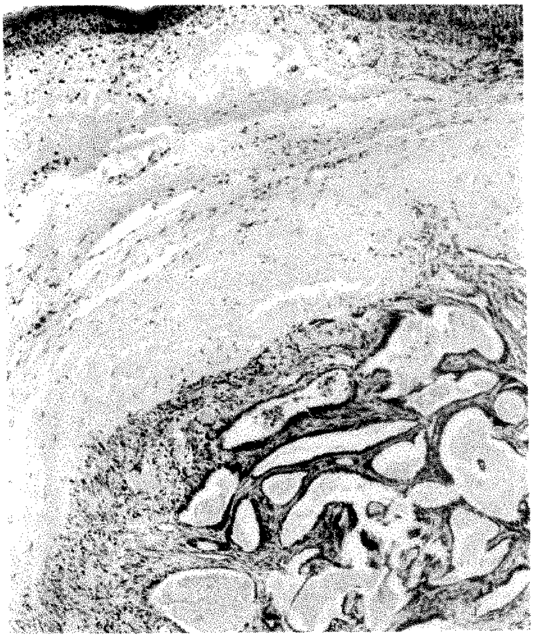

Fig 1. Parapharyngeal synovial sarcoma, separated from mucosa of pharynx by condensed fibrous connective tissue (H & E, original x80).

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.
REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

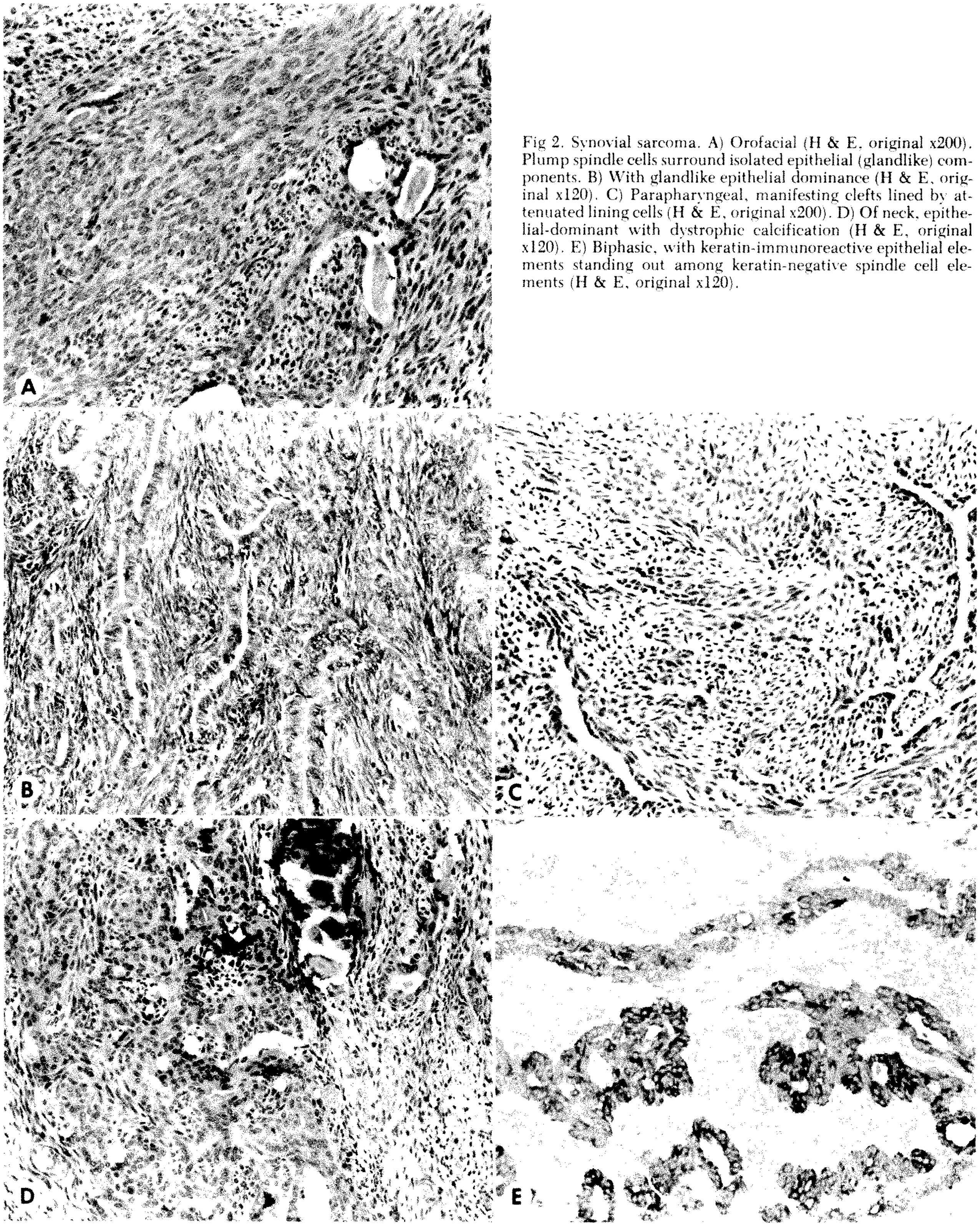

Fig 2. Synovial sarcoma. A) Orofacial (H & E, original x200). Plump spindle cells surround isolated epithelial (glandlike) components. B) With glandlike epithelial dominance (H & E, original x120). C) Parapharyngeal, manifesting clefts lined by attenuated lining cells (H & E, original x200). D) Of neck, epithelial-dominant with dystrophic calcification (H & E, original x120). E) Biphasic, with keratin-immunoreactive epithelial elements standing out among keratin-negative spindle cell elements (H & E, original x120).

The classic or biphasic synovial sarcoma is histologically characterized by a dual differentiation into epithelial nests and acinar collections in a fibrosarcomalike matrix (Fig 2A). The epithelial cells generally assume a glandlike configuration (Fig 2B). They may also be found lining clefts or artifactlike slits (a distinctive feature), arranged in solid aggregates, or forming papillary excrescences (Fig 2C). The glands and clefts often contain an eosinophilic material or debris that is typically mucicarmine-positive, periodic acid–Schiff–positive (before and after diastase), and Alcian blue–positive (before and after hyaluronidase). Reticulin stains can serve to highlight the glandlike structures when they are not readily apparent. The sarcomatous, spindle cell areas are composed of thin or plump cells arranged in fascicles. These are hyperchromatic, long, and sweeping or short and intersecting. Hyalinized collagen, at times amyloidlike, of varying prominence may separate the fascicles. Cellular density also varies, particularly in areas in which the stroma is myxoid or like a hemangiopericytoma. Calcification, either psammomatous or dystrophic, can be found in about a third of synovial sarcomas (Fig 2D). Extensive calcification is unusual, but thought by some to be a favorable prognostic indicator.[11] Cellular pleomorphism is usually minimal, and so, too, is mitotic activity.

Given the histologic display described above, diagnosis can be made with routine hematoxylin and eosin preparations. It is with the monophasic forms that diagnostic mischief can occur. In the seemingly wholly sarcomatous form, the diagnosis can be suspected from the appearance described above. The simplest method of confirmation is to cut additional sections in the hope of finding epithelial elements.

Since synovial sarcoma is relatively unique in its expression of epithelial cytokeratin antigens 7, 18, and 19 and epithelial membrane antigen, immunodetection of these cellular antigens (Fig 2E) can also confirm the light-optic impression.[8,12] Epithelial membrane antigen is said to be more sensitive.[8] Other epithelial markers, desmosomal plaque protein, desmoplakin, and desmoglein have also been reported to be present, but are less abundant than the keratin-reactive cells. The cells also express vimentin, but other intermediate filaments are absent. Other, far less cell-specific determinations such as Leu 7, *Ulex europaeus* I lectin receptors, and α1-antichymotrypsin may be positive, but these lack discrimination.[8] Electron-optic study is the third diagnostic measure that can be applied to the spindle cell, monophasic form of synovial sarcoma.[7,13] Fisher's[7] excellent exposition of the fine structure of biphasic and uniphasic synovial sarcomas clearly points to their congeneric origin.

Histogenetic unity is also supported by the observation that a specific reciprocal chromosomal translocation (X;18) is found in each form of synovial sarcoma.[14]

Despite relatively slow growth, the long-term survival data for synovial sarcomas at any site, including the head and neck, are not good. The Mayo Clinic's experience with the sarcoma, at any anatomic site, since 1960, indicates a 55% survival at 5 years and a 38% survival at 10 years.[15,16] The falloff at 10 years reflects the occurrence of late distant metastases, particularly to the lungs, between the 5th and 10th years after primary treatment. Roth et al,[3] Duvall et al,[17] and Moore and Berke[5] have all presented convincing evidence that the head and neck area is not a privileged site that imparts a more favorable outlook for synovial sarcoma. A life table analysis on 14 hypopharyngeal synovial sarcomas gives a 5-year survival of 36% and a 10-year survival of 18%.[17]

There have been several attempts to evaluate prognostic factors. The most relevant have been tumor size and extent (primarily depth) at time of primary treatment, with survival varying inversely to these two factors. Patient age at diagnosis appears to have a bearing, although the relative youth of patients with synovial sarcomas of the head and neck does not seem to impart a significantly better prognosis. DNA ploidy by flow cytometry is a significant objective probe. Sixty-seven percent of the synovial sarcomas studied by El-Naggar et al[18] had a diploid DNA content. This gave a marked advantage in survival over aneuploid synovial sarcomas. Interestingly, there were no correlations between type of ploidy and histologic subcategories (monophasic or biphasic).

We consider synovial sarcoma to be a high-grade malignancy irrespective of its phenotypes. Subtyping does not have an influence, independent of size, on patient survival, and grading based on mitotic count[19] and necrosis appears to be only marginally significant in prognosis.[18] Extensive tumoral calcification, an uncommon event, does appear to confer an improved outlook.[11]

Wide excision with negative margins remains the mainstay of therapy — not so easily achieved in the head and neck. Local excision is followed by a high incidence of local recurrence (60% to 90%), usually within 2 years.[19] Metastases to regional lymph nodes from synovial sarcomas in the head and neck are not often seen, even though the lymph nodes may be clinically enlarged.[20] Hematogenous spread is the harbinger of death and may be often delayed and occur without local recurrence. Preoperative or postoperative radiotherapy, with or without chemotherapy, may be responsible for the increase in survival statistics over the past two or three decades, but as Wright et al[15] point out, it is likely that the selection of patients for treatment is the most important factor.

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LARYNGEAL NEUROPROSTHESIS

The American Society for Artificial Internal Organs (ASAIO) is organizing a panel on Laryngeal Neuroprosthesis as part of its 38th Annual Meeting on May 8, 1992, at the Opryland Hotel in Nashville, Tennessee. Participants will be Michael Broniatowski, MD, Joaquin A. Hoffer, PhD, Christy L. Ludlow, PhD, and Gayle E. Woodson, MD. For further information, contact the ASAIO national office at (407) 391-8588, Fax (407) 368-9153; or Michael Broniatowski, MD, at (216) 363-2556.

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CONFERENCE ON ASSISTIVE LISTENING DEVICES
GENERAL ANNOUNCEMENT AND CALL FOR PAPERS

A Conference on Assistive Listening Devices, Tutorials, Applications, and Research will be held June 12-14, 1992, at The University of Iowa, Iowa City, Iowa. For information on registration and accommodation, contact the Conference Center, University of Iowa, Memorial Union, Iowa City, IA 52242; (319) 335-3231. Fax (319) 335-3407. For information on Call for Papers, contact Regina Tisor (319) 356-2471, Fax (319) 356-4547. We have applied for Continuing Education Units from ASHA and HAIC.

LETTERS TO THE EDITOR

To the Editor:

I recently read the paper by Weber and Koltai that was published in the August issue of the *Annals* (*Chlamydia trachomatis* in the Etiology of Acute Otitis Media, *Ann Otol Rhinol Laryngol* 1991;100:616-9). As an infectious disease pediatrician and chlamydia researcher, I found the study to be of some interest, but I think the authors are after the wrong chlamydia. *Chlamydia trachomatis* is primarily a sexually transmitted disease. Respiratory infection due to the organism is essentially limited to early infancy. Infants born to mothers with chlamydial infection may become infected in the eye or nasopharynx during delivery. The nasopharyngeal infection is usually asymptomatic and may persist for 3 years or longer. Only 30% or less of infants with positive nasopharyngeal cultures will develop chlamydial pneumonia, and only when between 1 and 3 months of age.[1] There is no epidemiologic evidence of horizontal or person-to-person transmission after delivery. There is also no convincing evidence that *C trachomatis* causes respiratory disease in children beyond early infancy, and that includes otitis media. The studies cited by Weber and Koltai are not equivocal, but lean to a lack of an association. The report of Banks et al (reference 11), which was only a letter to the editor, should not be considered seriously, because their laboratory methods are suspect. They did not "recover" the organism, but saw fluorescing green dots that they assumed were chlamydiae. Direct fluorescence antibody staining cannot be used to identify the organism in ear specimens, as it is neither sensitive nor specific. Weber and Koltai also failed to cite two other studies that did not find an association of *C trachomatis* with middle ear effusions in children. Hammerschlag et al[2] did not isolate *C trachomatis* from ear fluids of 68 children 9 months to 8 years of age. Blackston et al[3] also failed to identify the organism by tissue culture or direct fluorescence antibody staining in middle ear fluids of 48 children.

The only "real" report of the isolation of the organism from children with possible middle ear disease is the first, by Tipple et al,[4] in which *C trachomatis* was isolated from the middle ear aspirates of 3 of 11 infants with chlamydial pneumonia. These infants were all under 3 months of age and had the typical clinical presentation of infantile chlamydial pneumonia, which includes a considerable amount of upper airway congestion. This does not necessarily imply a causal relationship, since, as Weber and Koltai themselves state, the middle ear is continuous with the nasopharynx, and we know the organism is present in the nasopharyngeal mucosa.

Weber and Koltai also appear to be unaware of *Chlamydia pneumoniae*, the recently identified third chlamydial species that appears to be a primary human respiratory pathogen.[5] *Chlamydia pneumoniae* may cause 10% to 20% of community-acquired lower respiratory tract infections, including pneumonia and bronchitis. It may also cause some pharyngitis and sinusitis, and there is one report from Japan of the isolation of *C pneumoniae* from the middle ear aspirate of a 59-year-old man with otitis media.[6] Although infection with *C pneumoniae* appears to be most frequent in adolescents and adults, we have identified infection by culture in children as young as 14 months of age.[7] *Chlamydia pneumoniae* appears to be spread from person to person by respiratory droplets. Clearly, available clinical and epidemiologic data suggest that *C pneumoniae* is the chlamydial species most likely to play a role in otitis media in children.

Margaret R. Hammerschlag, MD
Depts of Pediatrics and Medicine
SUNY Health Science Center at Brooklyn
450 Clarkson Ave
Brooklyn, NY 11203-2098

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To the Editor:

It was with great interest and appreciation that we read the comments of Dr Hammerschlag, a known authority on chlamydia research, concerning our recent paper. We acknowledge and agree with Dr Hammerschlag's comments that *Chlamydia trachomatis* (CT) is a sexually transmitted disease and that a lack of evidence exists concerning horizontal spread. We also agree that CT may persist in the body for years, mainly asymptomatically. Unfortunately, this last statement cannot be made scientifically, since nobody actually knows the cause of every sore throat or adenoiditis in children. Perhaps CT is not as asymptomatic, during the 3 or more years that it is detectable, as we believe. In fact, it would not be unreasonable to assume that a CT-mediated nasopharyngitis may lead to a sterile serous otitis media.

The above statements, of course, could only carry meaning if CT was a viable pathogen. We agree with Dr Hammerschlag that controversy over CT as a pathogen for otitis media abounds and that all the studies cited had inherent flaws making the data suspect. It was on the basis of these controversies that we decided to at least prove or disprove that CT may be a pathogen in an animal model, despite the inherent risks in trying to extrapolate animal data to humans. We regret not including Dr Hammerschlag's paper, since we are well aware of it and this was an oversight on our part. The paper by Blackston et al was published after completion of our paper. Our paper was also completed before two other papers, which Dr Hammerschlag failed to mention, were published. These two papers[1,2] demonstrated positive CT culture in middle ear aspirates of children from 1 to 18 years of age. They also found positive cultures in tonsillar crypts and positive chlamydial antibodies. Indeed, CT may not be limited to infants as suggested by Dr Hammerschlag.

Unfortunately, Dr Hammerschlag's last paragraph is irrelevant to the context of our paper. We are indeed aware of *Chlamydia pneumoniae.* Two factors explain its exclusion from our paper. The first is that these papers were, again, published after our paper was completed. Second, our paper was on CT, not *C pneumoniae,* and we felt even during our revisions that it was inappropriate to mix the two and allow the opportunity for confusion. Indeed, Dr Hammerschlag is probably correct when she hints that *C pneumoniae* is most likely a major pathogen, while CT is not. This is an exciting area in which more basic science studies and clinical studies need to be completed. Thank you for allowing us the opportunity to respond to Dr Hammerschlag's comments.

Peter C. Weber, MD
Dept of Otolaryngology
University of Pittsburgh
Pittsburgh, PA 15213

Peter J. Koltai, MD
Dept of Surgery
Albany Medical College
Albany, NY 12208

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To the Editor:

I read with interest Drs Duncan and Eid's detailed article describing a case of bronchopulmonary dysplasia and accompanying tracheomalacia (Tracheomalacia and Bronchopulmonary Dysplasia, *Ann Otol Rhinol Laryngol* 1991;100:856-8). Their diagnosis was based on a flow-volume loop analysis and flexible bronchoscopy. I would like to add a cautionary note. In reviewing the flexible bronchoscopy performed on young children at St Christopher's Hospital for Children, collapse of the trachea on inspiration and a ballooning of the pars membranacea on expiration is a frequent finding, and it is tempting to make the diagnosis of tracheomalacia in the setting. It should be remembered, however, that in small children a flexible bronchoscope can of itself cause proximal obstruction to the flow of air within the trachea and cause this effect. With the emergence of both medical and surgical therapies for tracheomalacia in young children, accurate diagnosis is particularly important, and I would recommend a complementary rigid bronchoscopic examination when the diagnosis is in doubt.

Glenn Isaacson, MD
Dept of Pediatric Otolaryngology
St Christopher's Hospital for Children
Philadelphia, PA 19134-1095

To the Editor:

Thank you for giving us the opportunity to reply to Dr Isaacson's letter. The debate over the indications and efficacy in the use of flexible versus rigid bronchoscopy continues to rage. Certain advantages may exist for the use of flexible bronchoscopy, including eliminating the need for general anesthesia and assisted ventilation during the procedure, thus allowing visualization of tracheal dynamics without these complicating factors.[1,2] However, proximal obstruction from a flexible bronchoscope may occur, with resultant inspiratory collapse of the trachea. The index case was that of intrathoracic obstruction with resultant *expiratory* collapse of the trachea, suggested by flow-volume loops and further confirmed by elective endotracheal intubation. The clinical presentation, ancillary information, and judicious use of the flexible or rigid bronchoscope should eliminate the need for a second or complementary bronchoscopy.

Scott Duncan, MD
Nemr S. Eid, MD
School of Medicine
University of Louisville
Louisville, KY 40292

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2. Cohn RC, Kercsmar C, Dearborn D. Safety and efficacy of flexible endoscopy in children with bronchopulmonary dysplasia. Am J Dis Child 1988;142:1225-8.

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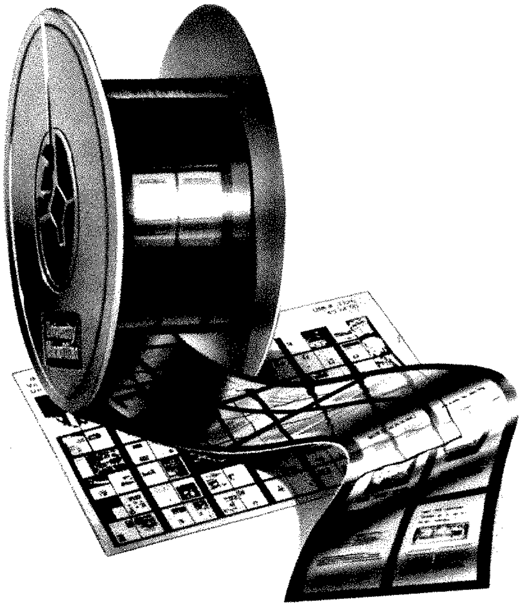

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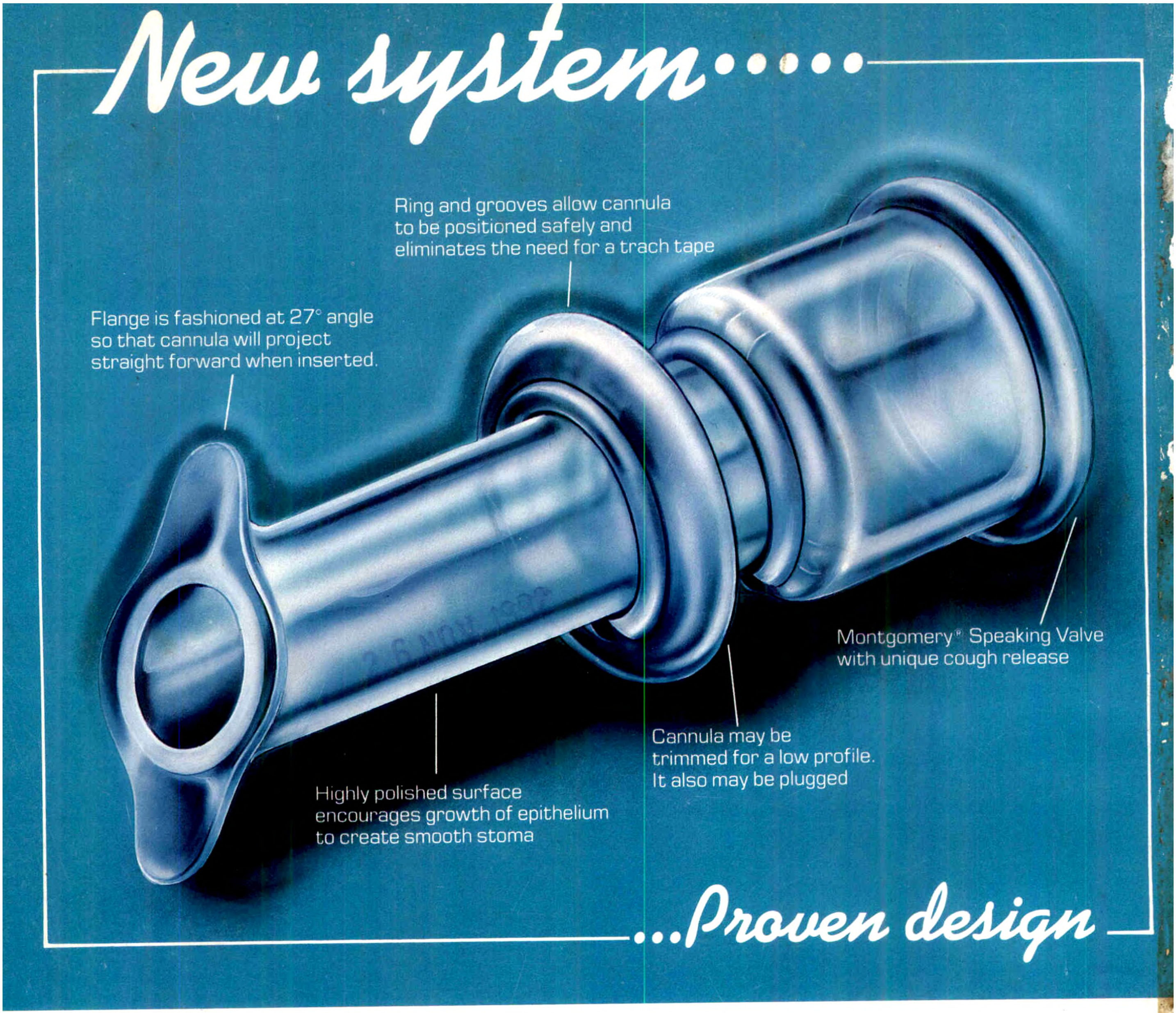

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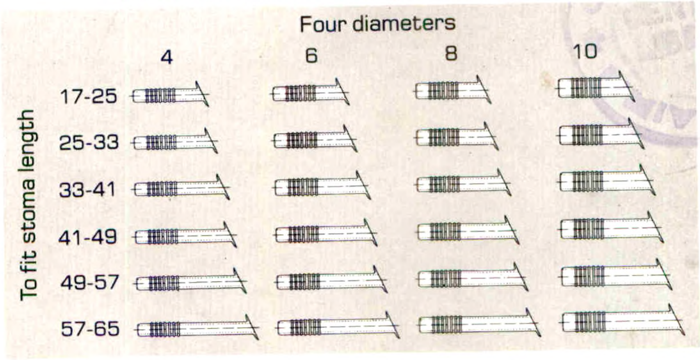

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